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TUMORS AND TUMOR-LIKE CONDITIONS OF THE LYMPHOCYTE, THE MYELOCYTE, THE ERYTHROCYTE AND THE RETICULUM CELL *

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During the seven years that the Lymphatic Tumor Registry ‡ of the American Association of Pathologists and Bacteriologists has been operating 380 cases have been contributed. Fifty of these cases were not tumor or tumor-like conditions of either lymphatic, hemopoietic, or reticulo-endothelial tissues. Of the balance all are of interest and value in the study of these conditions, but only about half of the total number have sufficiently complete records and material to permit the defining of the conditions present. Therefore, too few cases have as yet been contributed to the Registry to make statistical study of the individual conditions of much value in determining the age distribution, clinical character, course and outcome of each type of lesion. The cases most valuable to the Registry are those that have been followed to their conclusion, autopsy performed, and material furnished from biopsy and autopsy.

All cases in the Registry have been reviewed each year by the Registrar preliminary to rendering the annual report. All cases offering definite difficulties in diagnosis, in which adequate data and ma-

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‡ The Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists was established in 1925. It is now the Lymphatic Tumor Division of the American Registry of Pathology maintained at the Army Medical Museum under the auspices of the National Research Council. The committee for the Association consists of Dr. F. B. Mallory and Dr. James Ewing, to whom all difficult cases are referred. The author is Registrar and here expresses his deep appreciation for the invaluable coöperation of the committee, but assumes the entire responsibility for the opinions herein expressed.

terial were available, have been referred to the consulting committee and often to other pathologists. As a result of these studies points of importance in differential diagnosis have been brought out and it is believed that their presentation at this time may stimulate thought and discussion to the end that we may arrive at a classification of the tumor and tumor-like conditions of the lymphatic, hemopoietic and reticular tissues.

The nomenclature of these conditions in the textbooks and articles in periodicals is extremely variable, and there is a like variation in the nomenclature in the diagnoses received from the committee and from others who have examined the material. As is true of tumors of any structure there are many atypical cases, but there is little agreement in terminology. The data and illustrations in the literature are rarely adequate to define the entity presented, so that published reports have been found of little value in establishing a standard nomenclature. The cases forming the basis of this report are not all complete but were selected as conforming to types of which there are a sufficient number to be of value in classification.

In this discussion it is not considered wise to enter into the controversy concerning the ultimate origin of the cells concerned, but rather to consider the adult cell and attempt to define the conditions that arise from it. For this purpose the following stem cells each form a group and each group is subdivided into the types that appear to be represented in the Registry collection. These are the stem cells giving rise to the *lymphocyte*, the *polymorphonuclear leukocyte*, the *red blood corpuscle*, and the *monocyte* or reticulo-endothelial cell. It is realized that exception will be taken to the inference that the monocyte and the reticulo-endothelial cell are one and the same or that they have a common origin, but these neoplastic conditions present certain indications that such is the case.

It is not believed that there are any concepts in this article that have not been presented or at least suggested before. To trace these for priority of publication is beyond the energy of the writer and the scope of this article.

Lymphocyte

I. Lymphocytosis: Lymphoma

Unless the term *lymphoma* is applied to inflammatory reactions there are no cases in the Registry.

TABLE I

Classification of Tumors and Tumor-like Conditions of the Lymphatic, Hemopoietic and Reticular Tissues

Adult cell type	Lymphocyte	Myelogenous		Reticulum cell	
		Granular leukocytes	Red blood corpuscles	Reticulocyte monocyte	Hodgkin's disease
I† Reactions	*"Lymphoma" Lymphocytosis	Leukocytosis	Symptomatic polycythemia	*Gaucher's disease Niemann-Pick disease	Localized (sclerosing)
II Proliferations of neoplastic type	Leukemic lymphocytoma 1. Chronic 2. Acute	Leukemic myelocytoma 1. Chronic 2. Acute	1. Polycythemia vera (Syn. Erythremia 2. Leukemic erythrocytoma	Leukemic reticulocytoma (Syn. Monocytic leukemia)	←
III	Aleukemic lymphocytoma 1. Diffuse 2. Nodular	Aleukemic myelocytoma 1. Single 2. Multiple (Syn. Multiple myeloma)	*Aleukemic erythrocytoma	Aleukemic reticulocytoma	Generalized (cellular)
IV Malignant tumors	Lymphosarcoma 1. Aleukemic 2. Leukemic (Syn. Lymphatic leukosarcoma)	Myelosarcoma *1. Aleukemic 2. Leukemic (Syn. Myelocytic leukosarcoma) Chloroma	Erythrosarcoma *1. Aleukemic 2. Leukemic	Reticulum cell sarcoma	Sarcomatous

* Type not observed in Registry.

† Roman numerals refer to text heading.

II. Lymphocytoma, Leukemic — Syn. Lymphatic Leukemia

1. Definite leukemia, 25,000 or more white blood cells with a preponderance of lymphocytes. The number of cells varies in the individual case and from time to time in the same case. Also, cases that primarily are classified in the aleukemic group (below) may become leukemic and remain so, either after irradiation or spontaneously. The type of cells may be uniform or considerable variation may occur. The more numerous the younger forms, the more rapid the course of the disease and usually the younger the patient.

2. The enlargement of lymph nodes is usually generalized and the spleen, or liver, or both, usually are more or less increased in size. There may be an area of greater enlargement, especially in those cases in which the enlargement is the first symptom noted. This is true of those cases of aleukemic lymphocytoma that later become frankly leukemic. In general, the greater the number of lymphocytes in the blood the less the swelling of lymph nodes, and *vice versa*.

3. Microscopically there is an increase in the size of the primary nodules, due to proliferation of the lymphocytes. This proliferation finally obliterates the node structure so that it becomes a uniform mass of lymphocytes. In the liver the portal spaces are distended or enlarged by lymphocytes which also infiltrate between the liver cords. In the spleen the malpighian nodules are enlarged and encroach on the red pulp, often apparently obliterating it. In other organs diffuse infiltrations occur but these, even when grossly visible as pale areas, appear to be proliferations starting in preëxisting collections of lymphocytes. In this condition there are no true metastases. These infiltrations are more frequent and larger in the acute forms of leukemia. Some cases show many atypical cells and then approach the sarcoma type. Occasionally, cases primarily leukemic terminate in typical metastatic lymphosarcoma.

4. The reticulum of the nodes is not increased but is distended or separated by the lymphocytic increase.

5. Irradiation is effective in reducing the size of the tumors and the number of cells in the circulating blood. In many cases it appears to have increased the duration of life but it is only a palliative treatment and not curative.

III. Lymphocytoma, Aleukemic — Syn. Lymphatic Pseudoleukemia

(*a*) *Diffuse Type:*

1. Leukemia is absent but there are always abnormal lymphocytes in the blood if proper search is made for them. At times, and often throughout the course of the disease, there is an actual increase in lymphocytes. It is difficult to make a dividing line between the aleukemic and leukemic forms, as these merge into one another and the aleukemic form may become leukemic and, rarely, cases which when first observed have a leukemia of 25,000 or more may become aleukemic. For the purpose of this classification 25,000 or more white blood cells, with a preponderance of lymphocytes, have been considered necessary for the diagnosis of leukemia.

2. The swelling of the lymph nodes is less generalized than in the leukemic form and there is usually a region of greatest intensity. The spleen, or liver, or both may participate in the process.

3. Histologically the picture in the nodes may be the same as in the leukemic form, or a group of nodules may coalesce and leave some relatively unchanged node structure. This is especially true of the more rapid, fatal processes at the younger ages in which the cells often appear to be of unusually large size and show relatively frequent mitoses. Infiltrations are unusual and when present indicate an approach to leukemia or the presence of a leukemic change unrecognized before. It is not unusual to find evidence of a definite leukemia at autopsy, which had not been discovered in blood examinations. It represents a change subsequent to the blood examination last recorded and may have taken place within a few days of death. When atypical cells or many mitoses are found the condition approaches that of a lymphosarcoma which is sometimes the terminal picture in this group.

4. Reticulum the same as in the leukemic form.

5. Irradiation is effective in reducing the size of the nodes as a palliative measure. Following X-ray these cases may become leukemic.

(*b*) *Nodular Type — Syn. Giant Follicular Hyperplasia with Splenomegaly:*

1. The blood changes are similar to those in the diffuse form (above) but apparently leukemia develops less frequently.

2. The swelling of the lymph nodes is the same as in the diffuse form and is sometimes quite generalized. The spleen has always been involved, and in two observed cases was apparently the only focus of the disease.

3. Histologically the condition is characterized by large nodules, which appear to be of a secondary type, and an apparent increase in their number. The nodules are composed of the large type of lymphocytes, among which are rather numerous mitotic figures. The nodules may be contiguous and rarely appear to have coalesced, though there is often marked variation in size in the same section. These nodules are surrounded by relatively normal lymphocytes of the smaller size.

These individuals either die rather quickly or, if life is prolonged, the process terminates in a definite sarcomatous change in which there are metastases. In this type the cells show more pleomorphism than in any other lymphocytic tumor, resembling to some degree the cell picture of sarcomatous Hodgkin's disease, with which the condition occasionally has been confused.

4. Reticulum is loose meshed as in the diffuse form, thus differing from Hodgkin's disease or Hodgkin's sarcoma (see below).

5. This condition is very sensitive to irradiation which, properly used, will prolong life for many years. Superficial nodes well radiated may never swell again. It is quite possible that this condition may be curable when localized and treated early by adequate irradiation.

IV. Lymphosarcoma

(*a*) *Aleukemic:*

1. Typically, there are no abnormal findings in the blood, but following irradiation this form may become leukemic (see (*b*) below).

2. Tumors are localized and infiltrate, metastasize, or both. Metastatic nodules are found in situations where usually lymphocytic groups do not occur, as in the intermediate zone of the liver, the lower cortex of the kidney and the heart muscle.

3. Histologically the tumor itself is made up of atypical lymphocytic types with irregular nuclei and scanty cytoplasm. Mitoses are usually abundant. The more atypical the cells, the more malignant the tumor. Following irradiation the cells may become more typical.

4. Reticulum is loose meshed, as in the preceding types.

5. Very sensitive to irradiation, so much so that it is possible that taken early and adequately treated the tumor may be cured.

(*b*) *Leukemic — Syn. Lymphatic Leukosarcoma:*

1. Leukemic blood with a considerable proportion of abnormal young or embryonal types of lymphocytes. The leukemic condition in lymphosarcoma may be spontaneous, may follow irradiation, or a leukemia may terminate in a sarcomatous spread.

2. Local tumor mass invading, metastasizing, or both, with metastatic nodules as in the aleukemic form. In addition gross infiltrative types of spread may be found, as in ordinary leukemia.

3. Histologically the cells are atypical, as in the aleukemic form. In those cases that are primarily aleukemic but become leukemic after irradiation the cells become more typical.

4. Reticulum as in the other lymphocytic groups above.

5. Sensitive to irradiation to some degree but many cases terminate so quickly that no adequate data have been accumulated. The cases that have become leukemic after irradiation appear to be less sensitive than the aleukemic form and it is possible that the leukemic change in these is the result of inadequate or improper irradiation dosage.

The group of conditions arising from the lymphocyte or its stem cell is the best defined and best understood of all the groups here considered. The term lymphoblastoma may be applied to the entire group, but the different members must be otherwise designated as the term does not sufficiently define the entities. As there are no benign, non-inflammatory lymphomas in the Registry the criteria have been omitted but the condition has been placed, together with lymphocytosis, in the reactive group. Lymphocytosis is represented by several cases of glandular fever, the cell picture of which is that of a lymphocytic proliferation with active hyperplasia of the secondary nodules.

The rest of the group is familiar to most, under a variety of names which sometimes vary because of minor cytological or clinical differences, though more often nomenclature depends on previous instruction, either undergraduate or postgraduate. The simplest and shortest terms have been preferred in this work and the prefix "a" is sufficient to differentiate the leukemias from those conditions that are quite similar except for the absence of an appreciable increase of

cells in the peripheral blood. The term pseudoleukemia, also, is quite acceptable as accurately descriptive. The term "aleukemic leukemia" certainly has nothing to recommend it, even though there are phases in leukemias during which the leukemia is diminished or absent. Such phases, whether the result of treatment or not, can be designated as such without the use of a name suggesting a change to a different disease.

In this group arising from the lymphocyte there is considerable shifting from one subdivision to another, both spontaneously and as a result of irradiation. For instance a leukemia may terminate in a lymphosarcoma, or may become aleukemic. Leukemic or aleukemic lymphocytoma may become sarcomatous. In all aleukemic cases in the Registry from which blood films have been furnished abnormal lymphocyte types have been found, while frequently during the course of the disease a definite lymphocytosis is present even though a frank leukemia never appears.

Lymphosarcoma usually appears and continues as such. Occasionally, as indicated by the literature, a combination of a metastasizing tumor and a leukemia occurs (leukosarcoma) and may be the condition discovered at primary examination. In the Registry material a condition of leukemia has followed irradiation of lymphosarcoma in six instances and in these the progress of the disease has appeared to have been retarded as a result of the change.

The liver is an important organ to study in the differentiation of types. In the lymphocyte group there is a general proliferation of the lymphocytes in the portal areas, increasing the size of these areas either with or without infiltration between the liver cords. The infiltration is present in leukemia and this finding at autopsy always suggests that whatever may have been the findings in the blood a leukemic condition had existed perhaps only near the termination of the illness.

In this classification the extension of the process to other nodes or lymphocytic tissues is not considered a metastasis. Whether this spread is the result of a stimulus in the circulating blood or whether it is due to cells from the original process reaching the new areas by blood and lymph, and there only finding satisfactory conditions for growth, is not known. The latter alternative seems the more probable method.

Granular Leukocyte

I. Leukocytosis of the Granular Leukocytes

II. Myelocytoma, Leukemic — Syn. Myelogenous Leukemia

1. Definite leukemia, 25,000 or more white blood cells with a large proportion of myelocytes. The number of cells in the blood varies over a rather wide range even in a single case, and there is also a variation in the relative proportions of the different myelocyte types. In some cases, with or without treatment, the number of cells may decrease to a very low total, though more often the reverse is true. The greater the variation in cell type, usually, the more rapid the course of the disease.

2. The bone marrow shows marked myelogenetic activity and, therefore, there is a decrease in the red marrow. The spleen is markedly enlarged in most cases and the nodular markings are obscured. The liver is also enlarged to varying degrees. Lymph nodes usually do not participate in the swelling. Sometimes infiltration deposits are visible grossly in the tissues.

3. Microscopically there is marked myelogenetic activity in the bone marrow. The proliferating cells replace the marrow fat and crowd the erythrogenetic tissue. There is no bone destruction. In the spleen myelogenesis is usually active and takes place in the red pulp. It crowds and compresses the malpighian nodules and practically obliterates some of them. In the liver there is a diffuse infiltration, usually somewhat more marked in and near the portal connective tissue, but there is no great enlargement of these areas. Infiltration is more or less generalized and often relatively large masses are formed which suggest metastatic tumor. Where lymph nodes appear enlarged the histological picture is that of an infiltration, as in other organs. Occasionally leukemias become definitely sarcomatous and thus would be finally classified in Group IV, below.

4. There is no increase in reticulum in the marrow, though the spleen, especially after irradiation, shows some increase in fibrous tissue.

5. Irradiation is effective as a palliative measure in many cases. In the more acute forms it often appears materially to retard the process.

III. Myelocytoma, Aleukemic ((a) Single, (b) Multiple) — Syn. Single and Multiple Myeloma

1. Aleukemic but young cells are usually present in the blood and leukemia may occur during the course of the disease.

2. (*a*) Single myeloma occurs in long and flat bones where it produces definite tumors of osteolytic type without much tendency to spontaneous fracture.

(*b*) Multiple osteolytic tumors of the marrow, destroying the bone from within and leading to spontaneous fracture which is often the first definite symptom.

In both single and multiple myeloma there are no true metastases, though the invasiveness of some of them approaches the sarcoma type and sarcomatous changes may occur and metastases take place.

3. Microscopically the cells composing these tumors show considerable variation between different cases but tend to be rather uniform in the individual case. The most uniform picture is that of the so-called plasma cell type which is found in both the single and multiple form. Others show some variation in cell size and staining characteristics. Variation in size is an indication of greater malignancy, an approach to the true sarcoma in which there may be extreme variation in size and form.

4. No reticulum is produced by the tumor cells, though there is some supporting reticular tissue accompanying blood vessels.

5. These tumors are sensitive to irradiation but to what degree cannot be decided by the few cases in the Registry.

IV. Myelosarcoma

(*a*) *Aleukemic:*

This has not been observed in the Registry material. It is possible that this form is represented by those cases of single and multiple myeloma that invade other tissues without metastasis. The metastatic myelogenous neoplasms in the Registry have all been leukemic.

(*b*) *Leukemic — Syn. Myelocytic Leukosarcoma:*

This group includes the "green" tumor, chloroma.

1. The blood shows a definite leukemia in which there are many embryonal types of cell. The total count varies but is not often as high as in the chronic leukemias.

2. Aside from the bone marrow changes, which may be evenly generalized or have a focus of greater intensity, there are growths from the bones into adjacent tissues and metastatic deposits in parenchymatous organs. The primary spread from the bone, the metastases, or both, may show the green color characteristic of chloroma.

3. The cells are always more varied in form and staining than in the non-sarcomatous type and if a sarcomatous change occurs in a case of simple leukemia there may be found a definite focus of sarcoma type in the bone, surrounded by the usual picture found in simple leukemia.

4. Reticulum is not formed by the tumor cells.

5. Radiation sensitivity not determined by Registry material or literature. Theoretically this group should be sensitive to irradiation, but the course is usually so brief that no adequate data are available.

The stem cell for the granular leukocyte gives rise to the myelogenous, myelocytic leukemias, the aleukemic myelomas and the myelosarcomas or metastasizing myelocytic tumors. This group shows less shifting from one group to another but occasionally a sarcomatous change occurs in a myelogenous leukemia and likewise a leukemia may develop in an aleukemic myeloma. The principal difficulty in this group is the question as to which types are sarcoma. Both single and multiple myelomas destroy bone and by this invasiveness to some degree merit the term of sarcoma; but, the lymphocytomas by pressure may destroy neighboring tissues and the cells invade the repair-like process at the periphery of the growth. When single or multiple myelomas break through the bone and invade surrounding tissues they may be considered as truly malignant and therefore could be considered as belonging to the group of aleukemic myelosarcomas.

Aside from the multiple myelomas the sarcomatous myelocytomas in the Registry have all been leukemic. Chloroma is represented. The green pigmentation is occasionally present in the more malignant myelomas without leukemia.

In the leukemias the infiltrations are difficult to differentiate from true metastases. It is of little practical importance to make this differentiation. Infiltrations are usually more frequent and extensive in the cases clinically more malignant.

In the liver infiltrations are more prominent in and near the portal areas, but masses of considerable size are not found, as in the lymphocytic type. Sometimes lymph nodes show considerable enlargement as a result of infiltrations. Such infiltration is diffuse and the architecture of the node is preserved.

In myelocytic leukemia the blood film often shows considerable numbers of immature red corpuscles and nucleated cells of the "blast" type. This appeared to be compensatory, or at least consistent with the idea that parts of the marrow are forced to overwork and throw out immature forms in the effort to compensate for marrow destruction or replacement by the granular myelocytic proliferation.

Red Blood Corpuscle

I. Polycythemia, Symptomatic

An increase in the red corpuscles of reaction origin due to some definite and readily determined cause, such as being in high altitudes.

II. (a) Polycythemia Vera — Syn. Erythremia

This condition is suggested for this position as the analogue of chronic types of leukemia.

1. Increase of red corpuscles in the blood. Platelets are increased and, especially in the later stages, there is an increase in granular leukocytes which might be considered as analogous to the appearance of considerable numbers of "blasts" in myelocytic leukemia.
2. The bone marrow shows erythropoietic hyperplasia. The spleen is enlarged, usually with relatively little evidence of erythrogenesis. The enlargement appears to be due to the increase in blood corpuscles in the red pulp.
3. Reticulum of the organs concerned shows no change.
4. Irradiation is apparently of little benefit.

(b) Erythrocytoma, Leukemic — Syn. Erythrocytic Leukemia

This condition, a leukemia of the precursors of the red blood corpuscles, the erythrocytes, is the analogue of the acute leukemias; that is, those in which a large proportion of the cells are of more embryonal type than those normally found in the circulating blood.

1. Definite leukemia, the cells of which resemble lymphocytes, have little cytoplasm, often appearing as naked nuclei. Many "blasts" are present, the larger types predominating. Many abnormal red corpuscles.

2. Bone marrow shows marked erythropoiesis, the yellow marrow being replaced. The spleen is enlarged sometimes to a considerable degree. Lymph nodes are sometimes slightly enlarged, particularly those of the abdomen.

3. Microscopically in the marrow there is a replacement of the fat by embryonal cells of the erythrogenetic group, with an apparent crowding of all normal marrow cells. Even the strands of erythrogenetic tissue seem less numerous than normal. The predominating cell is polygonal with a vesicular nucleus and considerable cytoplasm which is non-granular. The spleen shows a productive type of process in the red pulp, in which erythrogenesis appears to be active. Lymph nodules are crowded by the infiltration or proliferation and some appear to be obliterated. In the lymph nodes there is an infiltration between the lymph nodules and, in this infiltration and in the spleen, megakaryocytes in all stages of development are usually found. These cells in certain stages of development may be confused with the Dorothy Reed cells and a diagnosis of cellular Hodgkin's disease made.

4. No new reticulum is formed.

5. Irradiation sensitivity — no data.

III. Erythrocytoma, Aleukemic

There are no cases of this type in the Registry. The condition of erythroblastic anemia seen in the earlier age groups appears to satisfy the requirements of this position.[2]

IV. Erythrocytic Sarcoma

(*a*) *Aleukemic:*

Not observed in the Registry material. (See note above.)

(*b*) *Leukemic:*

This condition was distinguished from the leukemic erythrocytoma by the presence of metastases in the one case that has been observed. These metastases were small hemorrhagic nodules of erythrogenetic tissue.

The group of conditions arising from the stem cell of the red corpuscles is of particular interest because so few cases have been recognized. In this study the writer has used the term erythrocyte to indicate the nucleated form preceding the cell which after loss of its nucleus becomes the corpuscle. Other terms are difficult to adapt, but it is realized that erythrocyte is used as a synonym for red blood corpuscle.

In this group few will disagree with the placing of symptomatic polycythemia in the reactive position. It is also possible that eventually all cases of polycythemia vera, erythremia, can be so placed, but the blood, marrow and spleen in cases of erythremia are analogous in their enlargement and activity to the picture seen in chronic myelocytic leukemia. Careful study of the blood in erythremia occasionally shows blasts, while among the leukocytes are usually found atypical mononuclear cells which cannot be definitely placed in the myelocyte group.

The analogue of acute leukemia in this group is characterized by a leukemia of non-granular cells having little cytoplasm and which cannot readily be differentiated from embryonal lymphocytes. In addition, however, there are numerous "blast" types and many abnormal corpuscles. The bone marrow in general is red, but with pale areas or large involvements of solid tumor-like tissue replacing the normal marrow. In the spleen the change or proliferation is in the red pulp, there being no proliferation of the malpighian nodules.

In the spleen and to some extent in the lymph nodes there is active erythropoiesis, which in the nodes appears as a part of an infiltrative process composed of undifferentiated cells, erythroblasts and a diffuse infiltration of the mature forms, the red corpuscles. Except for the type of cell the picture is that of a myelocytic condition. Hasty examination of the blood film usually leads to a diagnosis of acute lymphatic leukemia. The marked tendency to hemorrhage and the large number of "blasts" in the film are the clues that suggest the correct diagnosis. The formation of typical adult megakaryocytes in the affected tissues is of value but also seems to confuse the condition with Hodgkin's disease. The lack of sclerosis and the infrequency of typical Dorothy Reed types is of assistance in differentiation. In the nodes the fact that the process is infiltrative and does not show proliferation of the lymphocytes of the nodules or the internodular stroma is an important differential point.

The Reticulocyte (Monocyte)

Certain reactive conditions show such a preponderance of reticular hyperplasia that they are placed in this group rather than in that of the lymphocyte. These include tuberculosis, leprosy, tularemia and some others. Hodgkin's disease is characterized by a reticular hyperplasia and the so-called Hodgkin's sarcoma is a reticulum cell sarcoma which shows more cellular pleomorphism than the typical reticulum cell sarcoma. However, as there is so much controversy as to whether the conditions generally diagnosed Hodgkin's disease are reactions to infection or are neoplasms, they are placed in a separate column but under the heading designating conditions of reticulum cell hyperplasia.

I. Reactive Reticulocyte Hyperplasias

Examples are tuberculosis, leprosy, tularemia, and possibly the conditions of unknown etiology — Gaucher's and Niemann-Pick disease, which appear to be hyperplasias of reticulum cells.

II. Reticulocytoma, Leukemic — Syn. Monocytic Leukemia

The existence of this condition is now well established. Only one case is included in the Registry.

1. Leukemia of large cells of monocyte type having oval, bean-shaped or irregularly lobed nuclei and considerable basophilic pale cytoplasm. These cells are most difficult to separate from myelocytes, and differentiation by the blood film depends on precise staining. The cytoplasm is more abundant than in myelocytes, the size is more uniform and good staining brings out their essentially non-granular character. Accentuation of the acidophilic dye may show fine granules close to the nucleus. Too few cases have been observed to make further suggestions as to their differentiation, but the vital stains should be of value.

2. The spleen, lymph nodes and lymphatic structures are enlarged to varying degrees.

3. Microscopically there is a proliferation of rather typical reticulum cells between the nodules of lymph nodes and at the periphery of malpighian nodules in the spleen. The lymphatic nodules are not increased in size. Mitoses in the case observed were rare.

4. The proliferation is characterized by a delicate meshwork of reticulum closely surrounding the individual cells.

5. Irradiation — no available data.

III. Reticulocytoma, Aleukemic — (Usually Termed Reticulum Cell Sarcoma)

1. The blood is aleukemic, though there may be an increase in monocytes, particularly after irradiation.

2. Enlarged lymph nodes without true metastasis.

3. Microscopically there is a diffuse hyperplasia of reticulum cells obliterating the node structure, with some areas and nodules of small lymphocytes remaining in the smaller and presumably more recently involved nodes.

4. Reticulum surrounds each cell, forming a delicate meshwork.

5. Sensitivity to irradiation not determined by Registry material.

IV. Reticulocytic (Reticulum Cell) Sarcoma

1. Aleukemic: Monocytes may increase in the blood following irradiation.

2. Enlarged lymph nodes, spleen, or both, with metastatic deposits, invasion of adjacent tissues, or both.

3. Microscopically the cells are atypical reticulum cells surrounded by a delicate meshwork of reticulum. The cells show varying degrees of abnormality up to extremely bizarre forms in the most malignant types. Invasiveness may be slight, but infiltrative metastases involving parenchymatous organs, and especially skin, are frequent.

4. The intimate delicate reticulum constitutes a most important differential point for the diagnosis of this condition and its separation from large-celled lymphocytomas and small-celled carcinomas.

5. Sensitivity to irradiation not determined in Registry material.

Hodgkin's Disease

There are two distinct clinical forms of this condition, which to a large extent is localized, spreads by continuity and to local lymphatic structures, and sometimes terminates in sarcoma. The other is the

generalized form which spreads to nearly all lymph node groups, to liver, spleen or both, though there is usually a focus of greater intensity or degree of swelling.

I. Localized Form

1. Blood changes not diagnostic. In febrile phases there is a polymorphonuclear leukocytosis, and particularly in the later stages or after irradiation there may be an increase in monocytes. Eosinophiles are often moderately increased.

2. Local swelling of lymph node groups with more or less fusion of the nodes. Frequent sites are neck, mediastinum and abdomen. In the thorax the process may invade the lung by continuity or extend along bronchial lymphatics. In the abdomen the liver may contain nodules here and there without generalized involvement. The spleen may contain irregular masses. Small nodes are pale pink and translucent, but soon show areas of yellowish opacity and softening. Spontaneously, and especially after irradiation, there is much fibrosis which in large amounts is almost cartilaginous in consistence.

3. The earliest changes are seen in small nodes, that is, ones recently involved by the process, as the larger nodes show such complete obliteration of their structure that the sequence of events cannot be followed. In these small nodes there is a proliferation of the reticulum of the internodular stroma and more or less proliferation of the lymphocytes of the primary nodules. Large cells are formed and later the typical multinucleated Sternberg cells. The process is usually quite definite in the internodular stroma before the proliferating reticulum cells appear in numbers in the lymph nodules, also the new reticulum is quite dense between the nodules before it invades these structures. The reticulum is gradually replaced by collagen though the remnants of the lymph nodules can usually be made out. The lymphocytes gradually decrease during this sclerosing process, which goes on more rapidly if irradiation is used. Necrosis varies in different cases and appears to start at the node periphery in the early phases. No node of small size which could be considered the starting point of a Hodgkin's process has been described. It is possible that the primary lesion is characterized by early necrosis and that the proliferative changes are secondary. These localized processes in the gross cannot be distinguished readily from tuber-

culosis, especially the extrapulmonary lymph node involvements which are not rare in the negro race. Microscopically the absence of tubercle formation and the cell picture serve to differentiate. A considerable number of eosinophiles is usually seen in the tissue, especially in the early cellular phase.

4. The proliferating cells form reticulum, which is gradually replaced by collagen in the sclerotic process. In nodes almost wholly sclerotic small areas of reticulum representing former lymph nodules are surrounded by dense, relatively acellular collagenous rings representing the internodular stroma.

5. Irradiation increases the rapidity of the sclerosis and reduces the size of the swelling, and at the same time reduces the hyperplasia, especially that of the lymphocytes.

II. (*See Reticulocytoma, Leukemic*)

III. The Generalized Form

1. Blood changes not diagnostic. Febrile attacks, as in the localized form, may be accompanied by leukocytosis of the polymorphonuclear variety, while irradiation may lead to considerable increase in the monocytes, or these cells may increase spontaneously.

2. Starting usually from some one area of enlargement of lymph nodes or spleen the process causes in a relatively short time a generalized enlargement of lymph nodes and lymphatic structures. The generalized enlargement of the liver is especially noteworthy, though not always present to a marked degree. Grossly the organ is not characteristic but often the enlarged portal areas are visible. This type remains confined to the lymphatic structures, does not invade and clinically resembles the aleukemic lymphocytoma (pseudoleukemia).

3. Histological examination shows a cellular picture with less sclerosis, especially in the form that involves the lymphatic structures of the intestine. In the liver practically every portal space shows reticulum cell proliferation with enlargement while the Kupffer cells appear to be more abundant. In the spleen the proliferation is around the malpighian nodules and sometimes extends into them and obliterates the structure. The red pulp is not affected, except by enlargement of the nodules. In the nodes the process appears to start in the internodular stroma where there is proliferation of reticulum cells, which produce abundant reticulum of looser mesh than in the

localized type. There are fewer typical Sternberg cells but the large uninucleated reticulum cells are abundant, quickly invade the lymph nodules and increase the amount of reticulum. Sclerosis is slow and in the intestinal involvements little if any collagen is laid down. Necrosis is slight or absent. Eosinophiles are rare or absent.

4. This condition is characterized by the formation of abundant reticulum. Under irradiation there is sclerosis and collagen formation, but otherwise there is less sclerosis than in the localized form.

5. Sensitive to irradiation to some degree, but the generalization of the process renders adequate irradiation impossible.

IV. Hodgkin's Sarcoma

1. No cases with leukemia have been observed.

2. Occasionally during the course of a focal or generalized Hodgkin's disease there may occur a metastasizing neoplastic process, a true sarcoma. This sarcomatous change may come early or late in the course of the disease. It is prone to occur earlier in the more cellular types of lesion and at the younger ages. It may be the termination of slow processes, particularly those of a focal or localized nature which have been kept, sometimes years, under a certain degree of control by irradiation.

3. The cell of this tumor is the reticulum cell. The microscopic picture is that of reticulum cell sarcoma, sometimes with little pleomorphism, though usually there is much more than in the typical reticulum cell sarcoma. Metastases in other than lymphatic organs show less pleomorphism and fewer infiltrating lymphocytes, though, like true lympho-epithelioma, Hodgkin's sarcoma and reticulum cell sarcoma, they usually show considerable lymphocytic infiltration.

4. The reticulum is the same as is found in reticulum cell sarcoma.

5. There are no data available on the sensitivity of this condition to irradiation.

In the monocyte or reticulum cell group the characteristic differential criterion is the production of argentophile reticulum by the proliferating cells wherever these produce tissue or, in other words, are not purely infiltrative. In lymph nodes this is best seen in the internodular stroma; in the spleen in the peripheries of the malpighian nodules. In the sarcoma types the entire node may be involved, or only a part, as in a metastasis. Most of the reticulum cell

tumors composed of uniform, atypical cells are sarcomatous in that definite metastases occur.

Group III, the aleukemic reticulocytoma, is usually considered to be sarcoma, but there are a few cases in which the lesions were confined to lymph nodes and the changes were very like those of monocytic leukemia.

Reticulum cell sarcoma really includes Hodgkin's sarcoma and it is a better term for the condition.

The two types of Hodgkin's disease described appear to the writer as quite different conditions. The localized type has all the characteristics of an infectious granuloma, more like tuberculosis than any other known disease. The generalized type is more a hyperplasia with lesions closely resembling the cellular phases of the localized form, but without the tendency to necrosis and sclerosis.

The localized form frequently shows hepatic involvement in scattered nodules or massive infiltrations, just as is sometimes seen in tuberculosis. The generalized form, however, when it involves the liver affects *all* the portal areas, the lymphatic structures of the liver, in a manner similar to the lymphocytic involvement of these areas in lymphatic pseudoleukemia.

The material reviewed is still too scanty to justify the placing of this generalized form definitely as an aleukemic reticulocytoma, but it appears quite possible that such is the case and that it is not a reactive hyperplasia. Likewise many more completed cases must be accumulated to establish definitely that Hodgkin's disease in any form is an infectious granuloma. Termination in a definite sarcomatous condition is certainly unusual for granuloma but quite frequent in hyperplasias of lymphocytic and myelocytic tissue. The search for an etiological agent is definitely outside the scope of this Registry.

Discussion

The foregoing statements are based on Registry cases in which adequate material and clinical data have been supplied. This classification is offered for criticism and to stimulate discussion and the contribution of cases which will either support, refute, or modify the opinions herein expressed.

Considerable evidence has been presented heretofore that these conditions are closely related and that there have been cases showing

transitions between the groups arising from the different cells. This is especially true of the condition termed Hodgkin's disease. There is no evidence in the Registry material that this occurs. The term Hodgkin's disease, in recent years, has been applied to conditions of various types because of the presence of large multinucleated cells, or because of the clinical similarity between the cases, just as Thomas Hodgkin confused several of the groups over 100 years ago. We have ignored the facts that practically any malignant cell in some phase of its malignancy may produce multinucleated forms and that the clinical symptoms of a neoplastic condition are dependent on the location of the involvement, rather than on the type cell of the growth. In the Registry material myelocytomas, both granulocytic and erythrocytic, reticulum cell tumors, sarcomatous and not sarcomatous, and aleukemic lymphocytomas, especially the nodular type, have been diagnosed Hodgkin's disease. It is believed that error in the original diagnosis is thus responsible for the confusion that has led to the conception that Hodgkin's disease may terminate in either the lymphocytic or myelogenous group.

As Hodgkin's disease in its malignant phase is a true metastatic tumor, or as a true metastatic tumor may develop during the course of typical Hodgkin's disease, we must determine what the cell is that forms this malignant condition. In the Registry group the cells of the metastases in the sarcomatous phase of Hodgkin's disease have produced abundant reticulum and have not conformed to the morphology of either lymphocytes, large or small, or any cell of the myelogenous group. None of the other groups, lymphocytomas or myelocytomas, both of the granulocyte and erythrocyte types, produces reticulum. Monocytic leukemias and the reticulum cell tumors produce it in abundance. In fact, many of the so-called Hodgkin's sarcomas cannot be differentiated from reticulum cell sarcoma. Hodgkin's sarcoma is often, but not always, more pleomorphic, while reticulum cell sarcoma sometimes shows considerable variation in the size and shape of the cells.

Skin lesions are occasionally found in all groups. Hemorrhagic types of lesion were present in all three cases of the erythrocyte group and are more frequent in the myelogenous than in the lymphogenous conditions.

The first phenomenon noted in reticulum cell involvements may be a skin manifestation, or the hyperplasia may appear to follow or

terminate a condition characterized by diffuse skin eruptions. Mycosis fungoides is allied to or is a type of the reactive Hodgkin's granuloma.

In general it has been found much more satisfactory to depend on the characteristics of the cell growth, its location and extension, than on the type of cell. Many of these cells cannot be distinguished from one another in the tissues, especially in the more or less atypical forms in which they occur in these tumor and tumor-like conditions.

It is fully realized that there are bizarre conditions arising from some of these cells that do now and will in the future defy classification. These often are seen in very early life and are rapidly fatal. Some may be embryonal tumors of a cell preceding any differentiation. Most of them are so malignant that death ensues before diagnosis or adequate study is made; however, most of this group of tumors and tumor-like conditions are proliferations of cells so far differentiated as to maintain certain diagnostic characteristics. Transformation of a cell that looks like a lymphocyte into a myelocyte, monocyte, and so on, may and probably does occur, but there is some doubt in such cases whether the cell was, in fact, a lymphocyte. Is it not more probable that it was a cell that could not be differentiated by the methods used?

It is of the utmost importance that adequate material, well prepared, be available for study, especially when one desires to classify the condition. A "chewed out" piece of lymph node or a poor section offers little possibility for diagnosis, except in the simplest cases. When lymph nodes are removed a large and small one both should be included. A well stained blood film is necessary.

Summary

1. A discussion of the tumors and tumor-like conditions arising from the stem cells of the lymphocytes, the granular leukocyte, the red blood corpuscle, and the reticulum cell or monocyte is presented.

2. A classification of these conditions is presented, based on a study of the cases of the Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists.

3. Certain criteria for the differentiation of the conditions are given in explanation or elaboration of the tabular presentation of the classification.

4. Certain evidence is presented that some conditions ordinarily classified as Hodgkin's disease belong to the reticulum cell group, either as reactive hyperplasias, aleukemic reticulocytomas, or reticulum cell sarcomas.

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1. Ewing, James. Neoplastic Diseases. W. B. Saunders Company, Philadelphia, 1931, Ed. 3, 382, *et seq.*

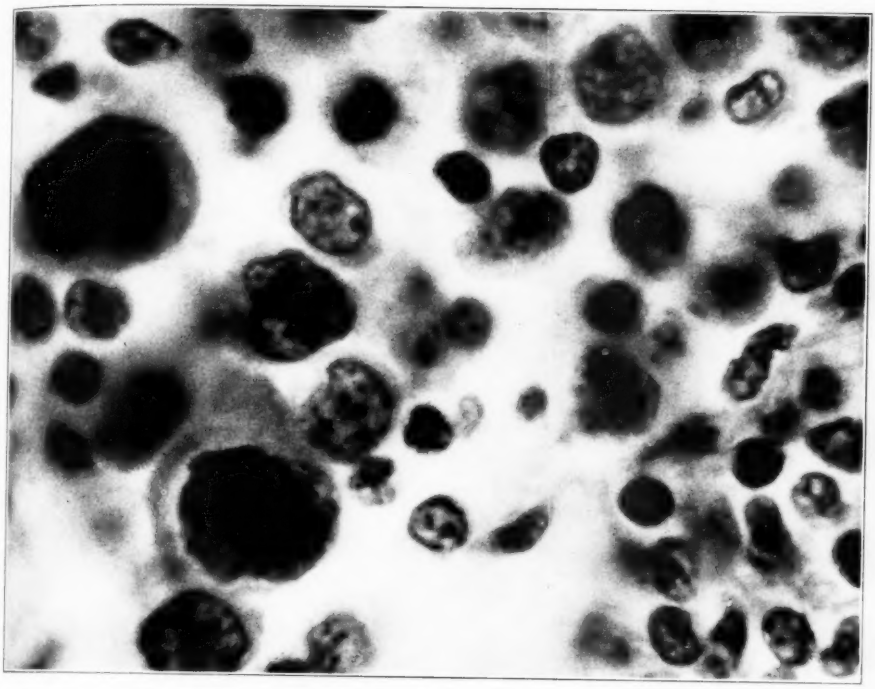
2. Ewing, James. Neoplastic Diseases. W. B. Saunders Company, Philadelphia, 1931, Ed. 3, 326.

DESCRIPTION OF PLATES

PLATE III

FIG. 1. Photograph of a section of lymph node from a case of lymphatic leukemia showing variations in cell size and giant cells. Hematoxylin and eosin stain.

FIG. 2. Reticulum stain from a section of the same node shown in Fig. 1. This is the characteristic reticulum of lymphocytic tissues. The lymphocytes do not form this reticulum. Similar reticulum is also seen in myelocytic hyperplasia. It is the normal reticulum of the node, produced by the reticulum cells. Compare with Figs. 6, 8, 10 and 12.



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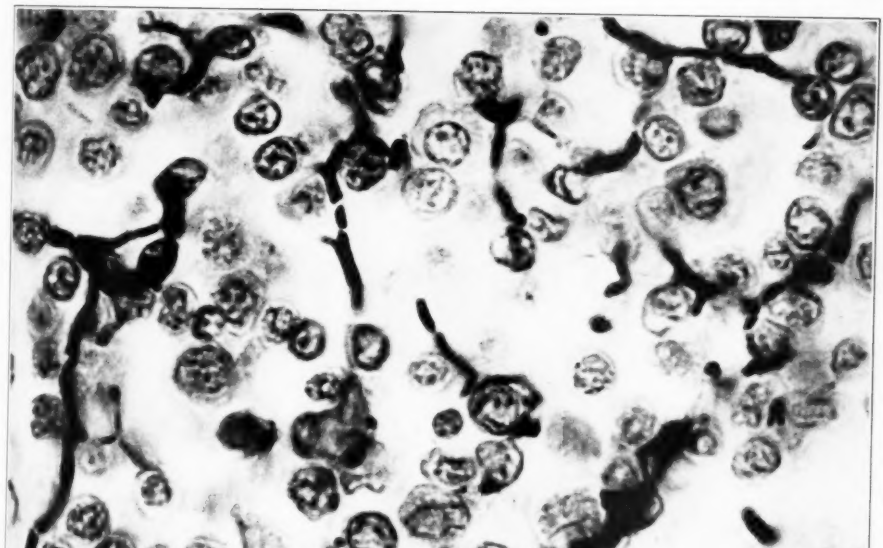

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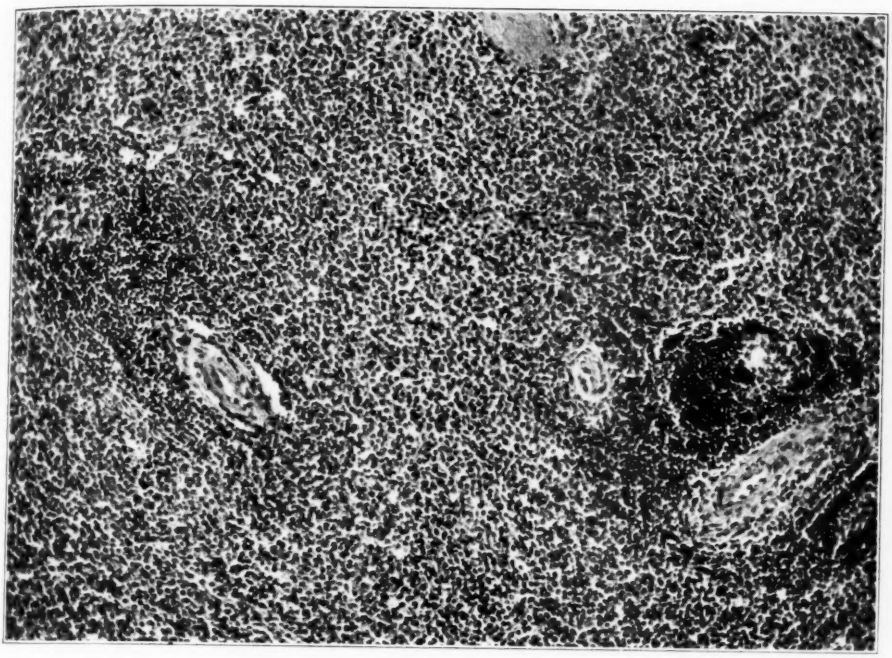
PLATE 112

FIG. 3. Spleen in myelogenous leukemia. Note the proliferation is between the nodules, which are somewhat atrophied. The change is in the red pulp, and differs distinctly from the change in lymphocytic proliferation in which the nodules are increased in size, encroaching on the red pulp.

FIG. 4. From a section of lymph node in erythrocytic leukemia to show typical megakaryocytes. Hematoxylin and eosin stain.



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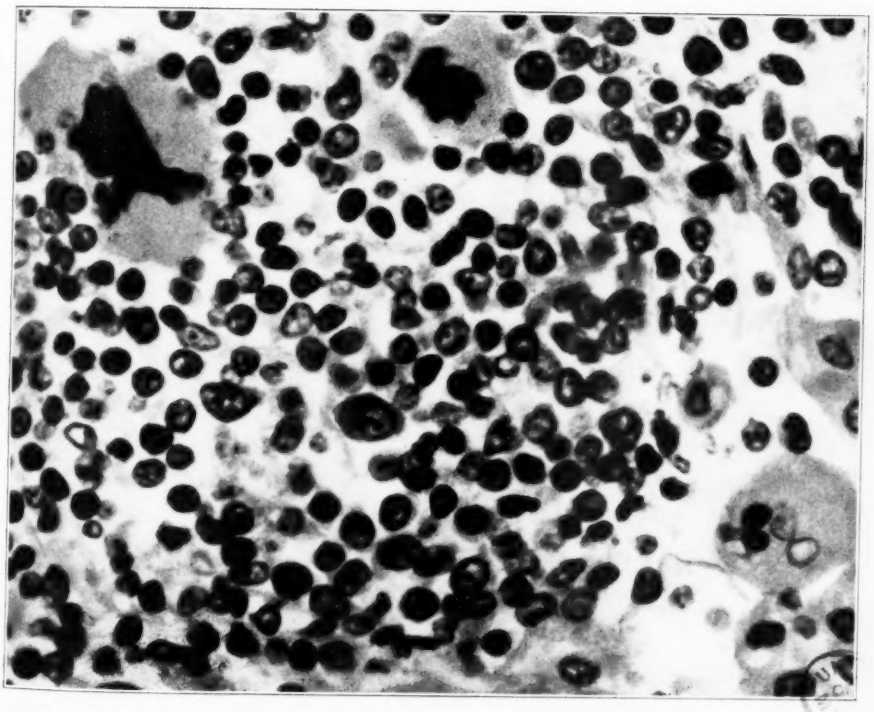

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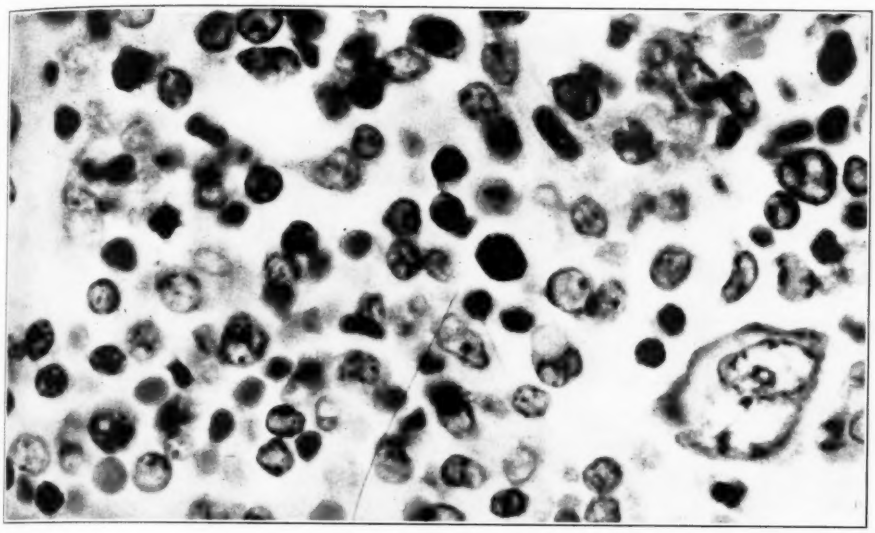
PLATE 113

FIG. 5. Section from the same node as Fig. 4. A young megakaryocyte is seen in the lower right hand corner. The pyknotic cells are "blasts." Note a diffuse infiltration of red blood corpuscles, a picture suggesting that these have been formed locally.

FIG. 6. Lymph node in monocytic leukemia stained for reticulum. Note the characteristic reticulum in close contact with the proliferating cells. Note also that the proliferation is between nodules or around them. This nodule is decreased in size and is invaded to a slight extent at the periphery by the proliferating cells and the reticulum they produce.



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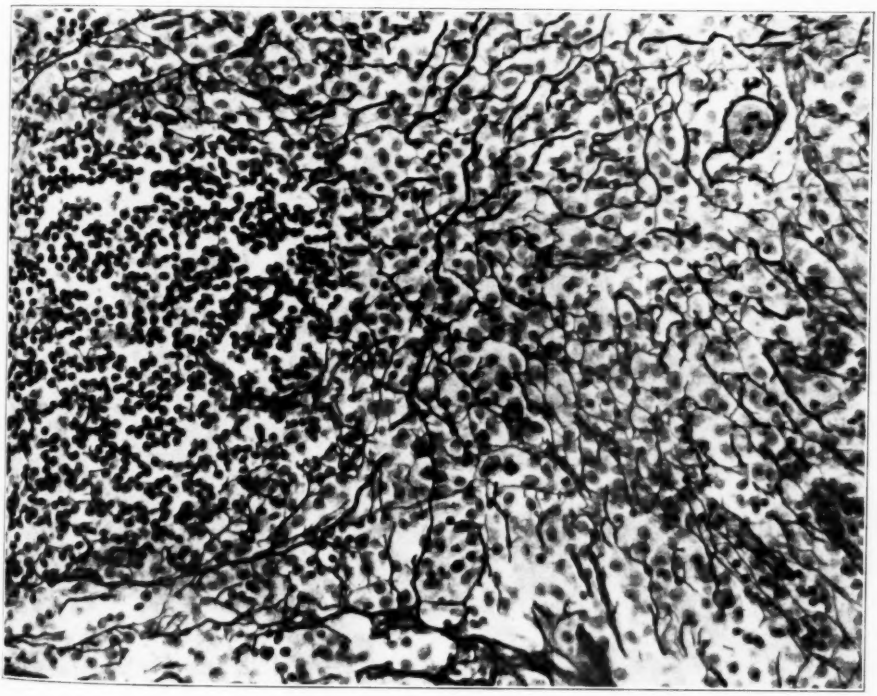

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PLATE 114

FIG. 7. Section of a lymph node from the same case shown in Fig. 6. Note the character of the cells. Without the help of differential staining of the intercellular reticulum it is difficult to differentiate such cells from large lymphocytes and marrow cells. Hematoxylin and eosin stain.

FIG. 8. Section from the same block as Fig. 7, stained for reticulum. Note the intimate relation of the reticulum to the proliferating cells. Figs. 6, 7 and 8 are from the same case.

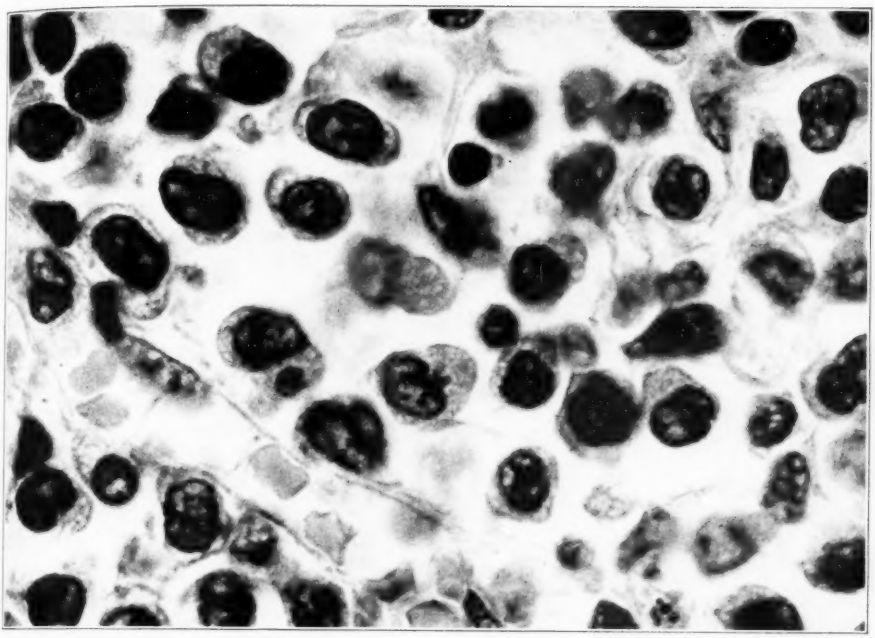

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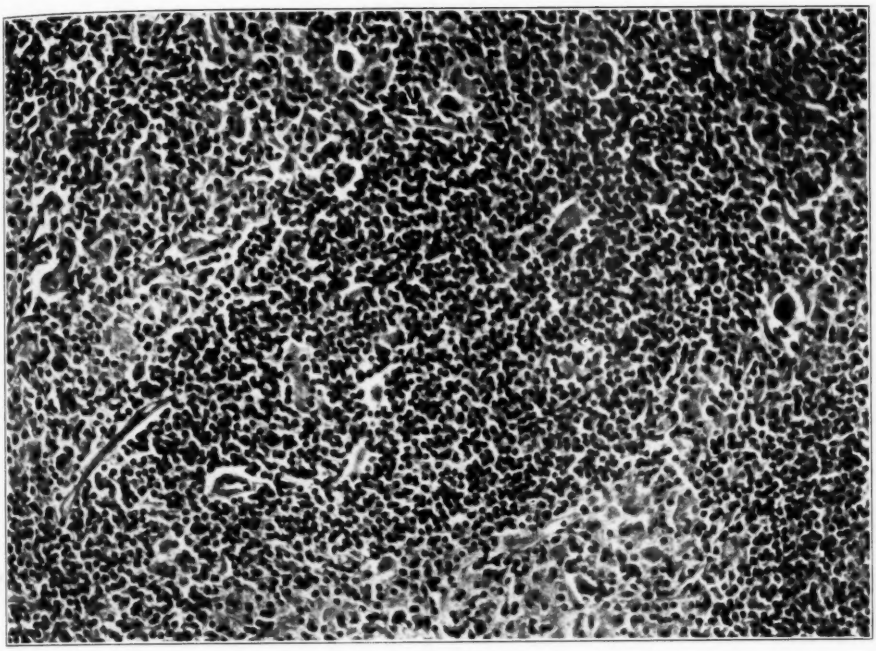
PLATE 115

FIG. 9. Spleen of Hodgkin's disease, reactive type. Note that the reticulum cell proliferation surrounds the malpighian nodule and has not involved the central part of the nodule. The nodules in this case were somewhat enlarged, as is frequently the picture at the beginning of the reaction. The decrease in nodule size appears to be due to the gradual encroachment of the process on the nodules, both in lymph nodes and in spleen, but the process starts as an extranodular reaction.

FIG. 10. Reticulum stain of a lymph node in the reactive type of Hodgkin's disease. Note the dense reticulum on the outside of the nodule shown in the upper and right hand portions of the photograph. The central and left hand portions are a part of a primary nodule, which at this time had become considerably infiltrated by the proliferating reticulum cells.



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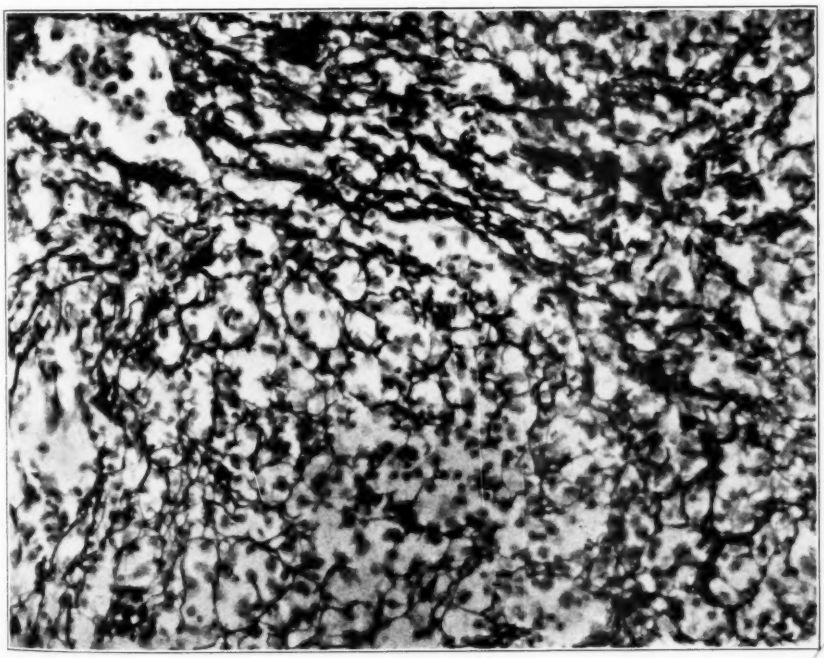

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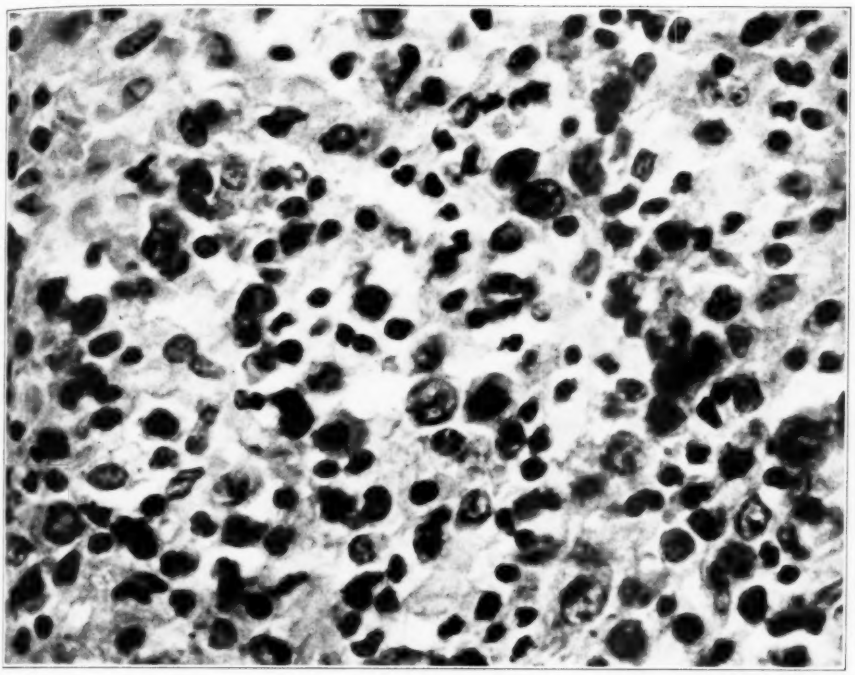
PLATE 116

FIG. 11. Section of a generalized Hodgkin's process. This is from a lymph node and shows the pleomorphic character of the process. Hematoxylin and eosin stain.

FIG. 12. Reticulum stain of a section from the same block as Fig. 11. This shows the characteristic reticulum of the diffuse Hodgkin's process and demonstrates the fact that it is a hyperplasia of reticulum cells.



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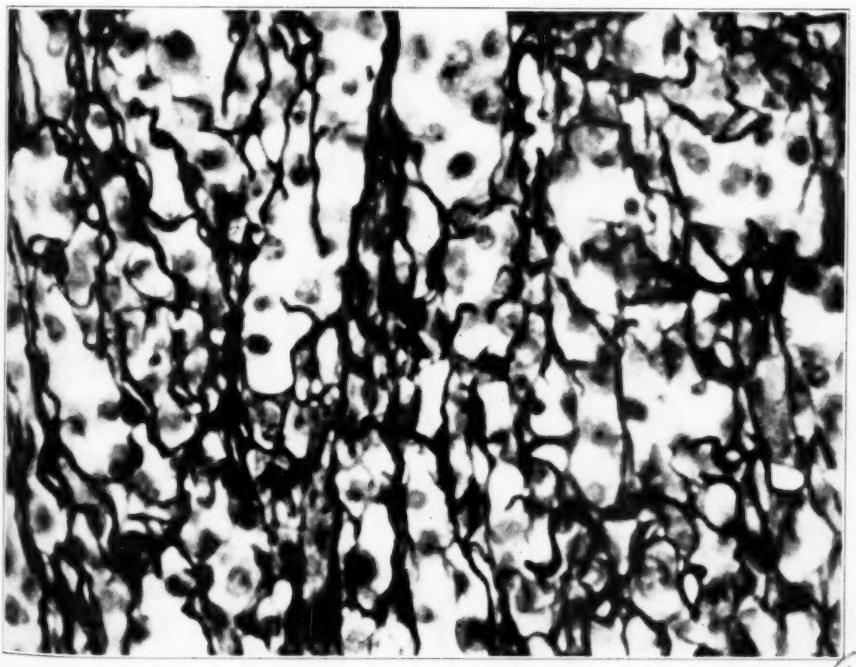

12

STUDIES ON THE MYOCARDIAL ASCHOFF BODY *

I. DESCRIPTIVE CLASSIFICATION OF LESIONS

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Although Romberg [1] in 1894 is generally considered the first to have described the inflammatory lesions in the myocardium now known as Aschoff bodies, it would appear that they were really first reported by Goodhart [2] in 1879. This author observed interstitial cell growth around vessels and between myocardial fasciculi in a typical case of rheumatic fever that showed at autopsy verrucous endocarditis (hempseed size) of the mitral and aortic valves, and in all probability a fibrinous pericarditis. As is well known, the association between rheumatic fever and cardiac injury was suspected and noted long before this. However, this short introductory review will deal only with the historical development of our knowledge of the myocardial Aschoff body and will accordingly be limited to those workers whose contributions in this field marked a definite advance.

In 1887 Cadet de Gassicourt [3] suggested that the inflammatory process in "rheumatism" starts in the depth of the muscular substance and is made evident by proliferation of interstitial tissue. In 1890 Krehl [4] made the significant observation that in a case of acute verrucous endocarditis there were present in the heart perivascular infiltration, increase in connective tissue and changes in the coronary arterioles which were, in all probability, the lesions at present receiving considerable recognition. Krehl observed these processes occurring more frequently in the left ventricle, particularly under the auriculoventricular ring.

Romberg [1] also noticed the preponderance of infiltration at the tendinous valvular insertion line and in the inner and posterior portions of the left ventricle. His observation of increased interstitial tissue and the presence of large cells is significant, as are his descriptions of vascular involvement. Three months later Bret [5] published

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a more detailed description, referring to the cells as "embryonnaire," an observation which, in the light of modern conceptions on the origin of the Aschoff body, was quite remarkable. Bret observed enlarged pyknotic nuclei, a peculiarity in the staining properties of the cytoplasm, the occurrence of a caseous material surrounded by these large cells, all lying between the muscle fibers — in short, a picture that undoubtedly represents the type of Aschoff body that will be described in this report as the coronal variety.

The previously mentioned authors, however, failed to make what turned out to be the most critical and important contribution in the study of these lesions, namely, their recognition as specific for rheumatic heart involvement. It remained for Aschoff definitely to establish a new era in the study of rheumatic fever when he announced that these lesions were specific for this disease. In Aschoff's [6] 1904 report, based on a study of 5 cases of articular rheumatism from a collection of 150 hearts studied by Tawara, he observed the characteristic nodules in 2. Aschoff described the simultaneous occurrence of blood vessel lesions simulating periarteritis nodosa, the submiliary size of these nodules, the tendency for the cells to assume fan and rosette arrangements around central necrotic areas, the large indented nuclei, the presence of giant cells and the peripheral zone of polymorphonuclear leukocytes and lymphocytes. He suggested the ultimate transformation of the nodules into connective tissue, thus predicting future descriptions of the life cycle of the lesion, and believed the characteristic cells arose from leukocytoid elements derived from the adventitial cells of the blood vessels.

The following year Geipel [7] gave an excellent detailed description of his findings in the hearts from 5 cases of acute verrucous endocarditis of rheumatic origin. Believing the cells to arise from connective tissue this author was of the opinion that the "rheumatic poison" affects connective tissue with resulting cellular reaction and breaking down of collagen and cell cytoplasm. He observed that the nodules occurred in the 5th to 6th week after the onset of the disease, that they can reach a breadth of 80 microns and a length of 880 microns, can occur in the interstitial as well as perivascular connective tissue, that the giant cells result from both multiplication of nuclei and confluence of individual cells, and that the ground substance eventually becomes fibrillar and transforms itself into connective tissue — a description that remarkably portrays one aspect

of the life cycle of the lesion as we know it today. Because of the fact, however, that Geipel observed similar myocardial nodules in a case of renal arteriosclerosis without a history of rheumatic fever (but with adherent pericardium) he came to the conclusion that these lesions were not specific.

In 1906 Aschoff and Tawara [8] reported 23 additional cases. In this paper the observation that the nodule did not bear as definite a relation to the blood vessels as had been stated before was recorded. They also added the description of the distinct nucleolus of the characteristic cell, mentioned the presence of mitotic figures and denied the origin of the giant cells from myocardium, mentioning the lymphocytoid cell as possibly giving rise to the characteristic cells. In the same year Aschoff [9] discussed the appearance of nodules in the conduction system. In 1907 Coombs [10] described the Aschoff body, confirmed its specificity and added the observation that the cytoplasm tended to be amphophilic. In 1908 Saigo [11] postulated an epithelioid and muscle cell origin of the Aschoff body. In 1909 Takayasu [12] described a variety of Aschoff body that will be reported in this paper as belonging to the mosaic type. This author did not consider the lesion strictly specific. In the same year Bracht and Wächter [13] emphasized one of the most important histological properties of the cell cytoplasm, namely its basophilia, and also laid stress on the subendocardial sites of these lesions. In his 1911 report Coombs [14] stated that the ground work of the Aschoff body may contain fibrin, that the auricles are rarely the site of these lesions and that the papillary muscles and septum usually escape the rheumatic damage, whereas the central fibrous body and the tissue around it are especially susceptible to the inflammation. In 1914 Thalhimer and Rothschild [15] again emphasized the specificity of the Aschoff body, mentioned the presence of several types of lesions in the myocardium, and described the "streamer-like" processes of the cytoplasm. In the same year Mallory [16] described the degenerated collagen fibers slowly attacked by endothelial leukocytes which sometimes formed giant cells.

In a discussion of a paper by Huzella [17] before the German Pathological Society in 1914 both Fraenkel and Aschoff again drew attention to the chief rôle played by connective tissue injury in the development of these lesions. In 1921 Fahr [18] compared the tissue changes in the myocardium and knee joints as they occur in scarlet

fever and in acute rheumatic fever. While pointing out certain similarities in the myocardial lesions he definitely considered that the qualitative and quantitative differences in the two lesions were sufficient to establish the rheumatic lesion as specific. In his 1924 monograph Coombs [19] expressed the belief that the characteristic cell in the Aschoff body developed from vascular endothelium.

In 1926 Sacks [20] published his excellent review on the pathology of rheumatic fever in which he suggested the subcutaneous nodule as a fruitful source for studying the origin of these cells by means of supravital stain technique. Sacks considered these cells as possibly arising from histiocytes. In 1929 Talalajew [21] made an important contribution to the study of Aschoff bodies, emphasizing again the important rôle of collagen swelling and necrosis and describing three phases in the life cycle of the lesion, namely swelling of collagenous bundles with exudation, proliferative processes with development of syncytial masses, and finally sclerosis. In this paper Talalajew attempted to correlate the evolution of the lesion with a time component. He believed that the first phase (exudative) may be seen at the end of the 2nd or 3rd week of the disease; the second phase (proliferative) may be completely developed at the end of the 1st or 2nd month and last, at times, for 6 months. The third phase (sclerosis) may appear during the 2nd month and may last for 6 months. In the same year Clawson's [22] observations led him to doubt the specificity of these lesions. He did not believe that they have distinctive histological characteristics and claimed that they are at times found in other diseases (subacute bacterial endocarditis, scarlet fever and syphilis). He observed all stages in the histological appearance of these lesions between polyblastic types and abscess-like forms. In the same year also, Gross, Loewe and Eliasoph [23] described unsuccessful attempts to transmit the disease to animals, laid down certain criteria whose fulfilment was essential in order to justify the claim, on a histological-anatomical basis, that the disease has been experimentally reproduced and, in a discussion on reported work, concluded that this disease as yet had not been successfully transmitted to animals.

In a report on the results of our studies on Aschoff bodies, presented before the American Association of Pathologists and Bacteriologists in 1930, we [24] described several types of Aschoff bodies probably representing different stages in the life cycle of this lesion.

We also described the development of a network of argentophilic reticulum fibers and emphasized the collagen swelling as the conspicuous feature of the early injury. Shortly after this Klinge [25] and his co-workers published a series of reports dealing with the pathogenesis of rheumatic fever in which, amongst other observations, they stressed fibrinoid degeneration of the ground substance as being the conspicuous feature of the early lesion (*Frühinfiltrat*). They also observed the characteristic silver-staining reticulum and described the Aschoff body in subacute and chronic stages, the healing scars and the lesions in the recurrent cases. They were strongly impressed by the allergic and hyperergic (Swift, Derick and Hitchcock [26]) concept of the origin of these lesions and believed that they had reproduced Aschoff bodies by properly sensitizing animals. They considered the characteristic cells to arise from the mesenchymal elements, a conception all the more interesting in view of Bret's hypothesis 35 years before this work appeared.

In 1930, however, Fahr [27] again emphasized the histological differences between the lesions found in scarlet fever and in rheumatic fever and denied the identity of Klinge's experimental lesions with those of true rheumatic fever. In 1932 McEwen [28] made supravital stains on scrapings from subcutaneous nodules. He concluded that the essential elements are cells arising from the mesenchymal elements of loose connective tissue, although endothelial cells may take part in this formation. These cells are characterized by their almost complete lack of phagocytic power and are not characterized by the reactions with neutral red which distinguish monocytes, epithelioid cells and clasmatocytes.

In his monograph on rheumatism published in 1933 Klinge [25] compiled the numerous reports published by himself and his coworkers and extended some of the observations. With regard to the life cycle of the Aschoff body he found that at the end of the 2nd week of the illness this lesion is represented by swelling of the "ground substance" of the collagen bundles, increase in connective tissue and wandering cells, with the presence of occasional giant cells. After the 4th week many swollen and multinucleated cells are found arranged either as a rosette around the swollen collagen, or dispersed throughout it. The center of the lesion gives a fibrin stain. The cells may show cytoplasmic streamers and present poorly outlined edges. An argentophilic reticulum is present. From this point

on, involutionary changes take place through the disappearance of the giant cells and fibrin and the development of connective tissue cells. In the last stages loss of the argentophilic properties takes place and the mass is converted into scar tissue.

It is obvious from this brief review that considerable obscurity still exists on the nature, histology and specificity of the Aschoff body. At least one of these points appears to be amenable to fairly exact study, namely, the histology of the lesion. It seems reasonable to assume that much of the confusion in the descriptive literature is due to the fact that different stages in the life cycle of the lesion have been emphasized by various authors as the typical Aschoff body. In this report we propose to present a simple histological classification and description of the lesions based on a study of 70 hearts obtained from cases in which diseases other than rheumatic fever could reasonably be ruled out. It will be seen that the lesions fall naturally into a few definite and more or less easily recognizable categories which, parallel clinical studies lead us to believe, reflect at once the stages in the life cycle of the lesion, as well as individual reactions of the given tissue.

So many authors have emphasized the dominant rôle played by injury to the collagen framework in the development of the Aschoff body that this can be considered an accepted fact. While a considerable concentration of collagen is found around blood vessels and in the subendocardium its distribution in the heart, considered as a whole, is not so widespread around the vascular bed and subendocardium as it is in the interstitial tissue between the muscle bundles. It is not surprising, therefore, that while the perivascular and subendocardial situations of the Aschoff body have been repeatedly emphasized in a considerable number of reports, many authors have observed that this lesion is by no means confined to these sites. On the contrary, even though they appear to be the sites of predilection in a number of cases, it would seem that the interstitial myocardial connective tissue is much more frequently involved. It is in this looser tissue that the lesions present a series of evolutionary phases relatively unhampered by dense collagen and elastic tissue and where, therefore, their life cycles can be traced in their more striking and characteristic forms. It is for these reasons that our descriptions and classification will be confined to the Aschoff body found in the interstices of the myocardial bundles. These will be referred to as

"myocardial Aschoff bodies," in contradistinction to the lesions found in the endocardium, subendocardium, adventitia of the blood vessels and in other organs. In the case of Aschoff bodies occurring in other organs the difficulty of obtaining sufficient material for statistical studies renders it inadvisable to attempt a classification at this time. In some tissue, *viz.*, subcutaneous nodules, tendon sheaths, and so on, legitimate doubts exist concerning the identity of these lesions with those found in the interstitial tissue of the myocardium. The nodules found in the adventitia of the blood vessels, endocardium, subendocardium and pericardium will be discussed briefly.

General Considerations

It has been mentioned already that the origin of the characteristic cell of the Aschoff body has been variously attributed to "leukocytoid elements" from adventitial cells, myocardial cells, epithelioid cells, endothelial leukocytes, vascular endothelium, histiocytes, "polyblasts," "lymphocytoid cells," connective tissue cells and undifferentiated mesenchymal elements. A careful study of considerable material indicates that only the three latter sources deserve serious consideration. While a study of subcutaneous nodules, as carried out by McEwen,[28] is of considerable importance, one cannot make the basic assumption that one is here dealing with a process identical with that occurring in the Aschoff body, even though the etiological agent is the same. Certainly, the subcutaneous nodule presents a histological appearance that is different from that of the Aschoff body, and apparently lacks the clear-cut specificity of the latter (Saphir and Wile [29]). It is important in this connection that of the eight authors cited by McEwen as discussing the origin of the characteristic cells in the Aschoff body, and in the subcutaneous nodules, seven suggest a different origin for each.

Studies on the Aschoff body very early in its development invariably disclose a swelling of the interstitial collagen fibers as the most conspicuous phenomenon. The lesion shows swelling and fusion of the fibers with development of intense eosinophilic properties. According to Klinge,[25] these fibers do not undergo dissolution. The ground substance swells, takes the picric acid stain with Van Gieson's method and stains with fibrin methods. On the other hand, argentophilic fibrils are preserved. With the resolution of the in-

flammatory process these newly acquired tinctorial properties disappear.

Even in these very early stages two distinct types of lesions are recognizable. One type, apparently arising in those areas where the collagen occurs in the form of relatively large compact masses, maintains for some time this dense collagenic structure and eventually gives rise to what we shall term the coronal Aschoff body (Fig. 1). The other type arises in the looser connective tissue where the collagen strands occur as more or less isolated fibers. This eventually gives rise to the reticular type of Aschoff body or "*Frühinfiltrat*" of Klinge (Fig. 2).

Simultaneously with the swelling of the collagen one observes a local accumulation of small round cells with spherical nuclei and extremely inconspicuous cytoplasm, indistinguishable from lymphocytes (Fig. 3). Whether these cells actually represent lymphocytes or originate from previously existing fibroblasts, or from histiocytes, *i. e.*, mature differentiated cells, or from the undifferentiated mesenchyme (Hueck [30]), it is as yet impossible to determine. It seems best, therefore, to designate these original cells as "mesenchymal cells" in order to avoid further controversy, bearing in mind the fact that this designation does not necessarily connote a direct derivation from the primitive mesenchymal system that has not passed through a differentiated cell stage (lymphocytes, fibroblasts, histiocytes). Already in this early stage Pap's [31] stain discloses the development of argyrophilic fibrils in close proximity to the proliferating mesenchymal cells, as well as along the swollen collagen fibers (in the reticular form).

Up to this point the lesion cannot safely be considered specific for rheumatic fever. Inflammatory lesions of the myocardium occurring in other diseases have also been seen to present interstitial collagen swelling with local cellular proliferation. In the case of the Aschoff body, however, additional phenomena appear from this point on; which, taken as a whole, present a picture that we have never seen in any disease where rheumatic fever may safely be ruled out. We must, therefore, conclude that they are absolutely specific for this disease.

With the introduction of the additional histological features (*vide infra*) which give the Aschoff body its strictly specific characteristics, development may take place along several different lines. The

histological structure of the lesion apparently depends on whether the Aschoff body originates from the dense or the loose collagen, on that phase of the life cycle of the lesion that is being studied, and also to some extent on the individual reaction occurring in the given case. A study of considerable material makes it clear that there is a consistency in the characteristics that these developing myocardial Aschoff bodies assume and, on the basis of the topographical relations of the cell and tissue structure, as well as on their tinctorial properties, the lesions may be placed into one of the following categories.

Classification of Myocardial Aschoff Bodies

1. Small cell coronal type
2. Large cell coronal type
3. Syncytial coronal type
4. Reticular type
5. Mosaic type
6. Polarized type
7. Fibrillar type

In the description of these types of Aschoff bodies mention will be made of their form. The question that naturally arises is whether this may not be influenced by the plane through which a given section is cut. It may be stated at once that our description is based on a reconstruction of the shape of the Aschoff body gathered from observations of the lesions, as observed in a great many sections and, in some cases, on the study of serial sections. From these studies it appears that while the nodules are at times spherical they generally take an oval, disk-like or spindle form. During the later phases of the life cycle of the lesion the disk-like and spindle forms predominate, finally elongating themselves into fusiform scars that lie in the interstices of the myocardial bundles.

Before entering into a detailed description of the various types of myocardial Aschoff bodies listed in our classification brief mention should be made of the histological characteristics of the Aschoff bodies situated in the adventitia of blood vessels and in the endocardium, subendocardium and pericardium. The topography of these lesions as a whole, as well as the relation of the cells to the collagen framework, is apparently determined by the density and

configuration of the tissue in which they lie (Gräff,[32] Darré and Albot [33]). Thus, the endocardial and subendocardial Aschoff bodies are represented by compressed, somewhat elongated lesions which tend to assume the form that will be called in this report the mosaic variety. The cells are scattered throughout the swollen collagen framework. If the collagen bundles are dense and compact the cells are irregularly compressed, assume bizarre polymorphous shapes, and may be connected to one another by delicate cytoplasmic streamers. As these Aschoff bodies pass through their life cycle, the cells change their shape and structure in accordance with the description that will be given for the myocardial lesions. The structure of the lesion as a whole, however, still remains that of cells compressed by a dense connective tissue.

In the case of pericardial Aschoff bodies the very loose milieu and the scarcity of collagenous bundles produce, during the early stages, a diffuse structure somewhat resembling the reticular type (*vide infra*). The development of the silver-staining lattice is not interfered with and the lesions show the tinctorial changes present in the myocardial nodules, the difference again being largely determined by the topographical relations of the cells to the surrounding tissue. The perivascular Aschoff bodies, on the other hand, generally occur in one of three forms, again determined by the consistence of the adventitial fibro-elastic tissue. A frequent form is the compressed mosaic type such as was mentioned for the endocardial and subendocardial Aschoff bodies. Here the Aschoff body appears to wrap itself around the vessel in the form of intercryptic cells compressed by dense connective tissue. Another form is in a looser mosaic pattern in which the cells predominate over the collagen framework. They are often large and appear frequently in giant cell form with the cells in fairly close juxtaposition. Finally, the parallel arrangement of the collagen fibrils along the course of a vessel not infrequently produces a picture that resembles the polarized and fibrillar types to be described. It should be mentioned again, however, that in spite of the configuration thus impressed on these Aschoff bodies by the state of the perivascular fibro-elastic tissue, the cells themselves undergo an orderly progression of changes similar to those that occur in the myocardial Aschoff bodies proper.

Finally, concerning the properties of all types of Aschoff bodies found in the heart, it may be said that, contrary to what has been

stated in the literature, these lesions rarely, if ever, show a fibrin constituent. Furthermore, the presence of the Aschoff body does not influence any elastic tissue present at the site of the lesion. Particularly during the stage of fragmentation portions of the swollen collagen may take the picric acid stain with the Van Gieson method. All stages of Aschoff bodies may show a mantle of polymorphonuclear leukocytes (neutrophilic and eosinophilic), lymphocytes, plasma cells and fibroblasts. These non-specific constituents of the lesion are generally found around the young fresh nodules so frequently seen in the myocardium of children. On the other hand, a variety of lesions which present no specific characteristics may also be found. These may vary from interstitial edema with relatively few wandering cells, to large collections of leukocytes, particularly eosinophiles (Wätjen [34]), even to abscess-like formation.

Mitotic figures occur with extreme rarity. On the other hand, dissolution of the Aschoff cells is not infrequently encountered. This is usually preceded by disappearance of nuclear chromatin, leaving nuclear ghosts in the form of more or less empty vesicles. Damage to the myocardium adjacent to the Aschoff bodies may be relatively mild. At times, however, considerable destruction takes place. The neighboring myocardial cells may appear hypertrophied, at times vacuolated, and may show complete dissolution and replacement by enormous scars. As a consequence, whereas the Aschoff body is essentially submiliary and visible only microscopically, the extensive scarring of the adjoining muscle, as well as fusion of neighboring Aschoff bodies, may produce lesions that are macroscopically visible (MacCallum [35]). It may be added that eosinophilic masses may be seen within the cytoplasm on rare occasions. These were considered by Coburn [36] to be engulfed collagen particles. Bacterial stains almost invariably show the lesions to be free of bacteria. The organisms that may rarely be seen can easily be accounted for as of postmortem occurrence.

Methods

The hearts were generally fixed in 10 per cent neutral formol-saline.* At times formol-Müller was used as a fixative. Before fixation blocks of tissue were removed and placed in 96 per cent alcohol and in Zenker's solution for special

* Solution of formaldehyde U.S.P. 10 parts, 1 per cent sodium chloride solution 90 parts. This solution is rendered neutral with a weak alkali.

staining purposes. For routine studies the standardized blocks of Gross, Antopol and Sacks [37] were cut after fixation and sections were stained with hematoxylin and eosin, and with Weigert's elastic and Van Gieson's connective tissue stains. In order to study the development of argentophilic fibers Pap's silver impregnation method was used. There were employed further, Masson's trichrome stains, Goodpasture's, and Brown and Brenner's bacterial stains, Mallory's phosphotungstic acid hematoxylin and Weigert's fibrin method. We have abandoned the Unna-Pappenheim methyl green-pyronin method inasmuch as in our hands this procedure has not given results that were in any sense superior to or more edifying than those obtained with a properly performed hematoxylin-eosin stain. In carrying out the latter attention should be paid to differentiating the hematoxylin-stained tissue in weak alkaline water. By this means the basophilic properties of the cytoplasm are brought out clearly, without losing the other important characteristics of the cells, namely the protoplasmic structure and the ragged edges.

Small Cell Coronal Type

This type of Aschoff body (Fig. 1) is generally somewhat ovoid in shape. Occasionally, round as well as more elongated forms are also encountered. Early in its development one may note in many examples of this type of Aschoff body a considerable accumulation of rather small cells (slightly larger than a lymphocyte) which form a generally compact mantle of varying thickness around a central mass of swollen eosinophilic collagen. Because of this peripheral situation of the cells with respect to the central collagen mass this type of Aschoff body will be referred to as the coronal type.

The collagen is, as noted above, swollen and eosinophilic. In most instances the fibers are fused into large irregular masses. The swollen collagen may be seen to be partially or completely broken up into fine or larger granules (collagen fragmentation). The cells are round or oval, the cytoplasm stains evenly, is generally basophilic and forms a delicate and distinct, smoothly outlined mantle around the nucleus. At times the cell may possess more than one nucleus (two or three centrally placed). These giant cells, however, occur less frequently in the small cell coronal type of Aschoff body than in any of the other types to be described, except possibly the fibrillar type.

The nuclei may occur in three forms commonly found in all varieties of Aschoff bodies. The type of nucleus found most frequently in the small cell coronal Aschoff body is round or oval with a delicate, sometimes folded nuclear membrane and a fine dust-like chromatin structure, which may at times show irregular concentrations or bar-

like arrangements with fine projections radiating from the bar. Because of its resemblance to the fibrocyte (fibroblast) this nucleus will be referred to as the fibrocytoid nucleus (Figs. 1, 4, 9, 10, 11). The next most frequently occurring variety is the owl-eyed nucleus (Figs. 4, 5, 6, 9, 11, 12). This has been termed "target" nucleus by Whitman and Eastlake.[38] It is generally somewhat irregularly circular, possesses a heavy nuclear membrane with a distinctly dark and, at times, somewhat stellate nucleolus. The space between the nucleolus and the nuclear membrane tends to be poor in chromatin material. This is well brought out by the Masson stains. In a considerably smaller percentage of the cells the nucleus is somewhat polymorphous in shape and generally quite large. It stains solidly and is therefore properly designated pyknotic nucleus (Figs. 11, 12, 15, 19).

The cells in this type of Aschoff body may be so numerous, and the collagen at times so scanty, that the impression given is that of a rather compact cellular subvariety. This type of Aschoff body not infrequently shows a fairly conspicuous mantle of leukocytes among the other layers of the small cells, spreading diffusely into the adjacent myocardium.

Large Cell Coronal Type

This type of Aschoff body (Figs. 4 and 5) is somewhat similar morphologically to the small cell variety. As its name indicates, the central swollen and at times fragmented mass of eosinophilic collagen is surrounded by a mantle of cells which possess much more abundant basophilic cytoplasm. The cytoplasm may be finely granular and not infrequently presents ragged edges, that is to say, the cellular outline tends to be indistinct, drawn out into pseudopods and broken up into granules. In this type the incidence of giant cells is larger than in the small cell coronal variety. As in most types of Aschoff bodies the giant cells are characterized by a central position of the nuclei. In the large cell coronal Aschoff body the giant cells are larger and may possess seven or more nuclei; the latter are round or oval and are irregularly arranged at the center of the cell. Silver stain reveals a definite reticulum in the proximity of these cells.

Syncytial Coronal Type

This type of Aschoff body (Fig. 6) occurs relatively infrequently and has been found thus far generally in acute cases. The conspicuous feature of this lesion is the development of an enormous syncytial mass, or masses, which apparently overshadow the scant central collagen material. The cytoplasm is extraordinarily abundant, basophilic, with indistinct and ragged outlines. Isolated fragments of cytoplasm are found. The nuclei are predominantly owl-eyed and appear to take a peripheral position within the cytoplasmic masses. Fibrocytoid nuclei also occur. Pyknotic nuclei are relatively infrequent.

Reticular Type

It has been mentioned already that the reticular type of Aschoff body arises in loose connective tissue. The framework consists of an interlacing mesh of swollen, eosinophilic collagen fibers showing fusion at points of contact (Fig. 2). In its more characteristic form the meshwork shows an orientation directed more or less along the planes of the adjoining myocardial bundles. However, variations occur in which the swollen fibers present no approach to an orderly arrangement, running in all directions and forming irregular clumps and tangles. Figure 7 represents an early stage in the formation of this type of lesion. In another variant the points of fusion may become quite extensive and give the impression of large eosinophilic collagenous masses (Fig. 8). However, one can always observe these masses passing imperceptibly into isolated, more delicate strands.

Silver impregnation of the reticular framework discloses argentophilic fibers overlying the net of swollen collagen. We have not been able to convince ourselves that these argentophilic fibrils lie actually within the swollen substance (ground substance?). Van Gieson's stain regularly discloses an admixture of yellowish and reddish fibers which are in places continuous with one another. Again, it is extremely difficult to determine whether the picric acid-staining material represents a substance (ground substance) essentially different from the fuchsinophilic (fibrillar) material.

This swollen reticulum frequently takes on the tinctorial properties of fibrin. In their configuration, however, the fibers can easily

be distinguished from fibrin. Furthermore, it can readily be determined that these "fibrinoid" fibers are continuous with collagen fibers in the vicinity, where they show the characteristic staining for collagen.

Contrary to the views expressed by Klinge, the collagen framework is at times seen to be extensively broken down and granular. In places this granular material, resulting from considerable fusion of the collagenic fibers, may present appearances that merge imperceptibly with variants of the mosaic Aschoff body types to be described.

Mosaic Type

This type of Aschoff body (Fig. 9) is the one most frequently encountered in the myocardium of the rheumatic heart. In contrast to the coronal types it consists of a more or less uniform distribution of collagen fibers and cells forming a mosaic pattern of the two components. Because of the variations in the proportions of collagen and cells, the size of the cells, the condition of the collagen and the manner in which the cells are lodged between the collagen masses, the mosaic forms may present a protean appearance. In one form the cells seem to be squeezed into the spaces or crypts between the collagen masses with the cytoplasm extending as streamers, which are sometimes extremely delicate, between the more dense and somewhat solid appearing, swollen eosinophilic collagen ground substance (Figs. 9 and 15). When these streamers form distinct cytoplasmic bridges between a number of the adjacent cells they tend to form large syncytial masses. In this mosaic type the cytoplasm is almost invariably deeply basophilic, the ragged edges are prominent, as is fragmentation of the cytoplasm and collagen. The argentophilic reticulum fibers are also quite prominent. There is a fairly even proportion between the owl-eyed and fibrocytoid nuclei. Pyknosis is not infrequently seen in this type.

In another variant of the mosaic Aschoff body (Fig. 10) the cells do not show the tendency to be compressed by swollen collagen masses, as in the variant previously mentioned. The cytoplasm is deeply basophilic and presents markedly irregular ragged edges. Both cytoplasm and collagen show considerable fragmentation. Indeed, the collagen may show such conspicuous granular degeneration as to be indistinguishable from the fused reticular type with granular

collagen previously described. A prominent silver-staining lattice is invariably present. It is this variant of the mosaic Aschoff body that has been loosely designated by a number of authors as the "typical" Aschoff body. Giant cells are not infrequently found. Owl-eyed nuclei occur with approximately the same frequency as that seen in the syncytial coronal type.

Polarized Type

This type of Aschoff body apparently represents a further stage in the metamorphosis of the Aschoff cells into fibroblasts. The topography of the lesion as a whole is that of a spindle-shaped or tapering disk-like mass representing many cells compressed between the myocardial bundles. The cells themselves vary from somewhat irregular elongated forms to spindle shapes, the difference probably depending on the maturity of the lesions. The irregular forms (Fig. 11) present ragged edges and are basophilic. The spindle-shaped cells (Fig. 12) also present a basophilic cytoplasm. The edges, however, are generally smoother and more sharply defined. The owl-eyed nuclei are still the predominating types but seem to occur somewhat less frequently than in the syncytial coronal or mosaic types. Pyknotic nuclei are seen with perhaps less frequency than in the types thus far described.

The collagen framework is generally delicate. While eosinophilic swollen fragments may be found the fibers show, as a rule, less swelling than in the other types. On the other hand, swelling and fragmentation may be occasionally quite conspicuous. The rather prominent argentophilic reticulum fibers show compression to conform with the spindle shape of the nodule as a whole (Fig. 13).

Another variety of the polarized type, which is not infrequently met with, may be called the "giant cell polarized type." In this form the Aschoff body shows a polarization into a rather short disk. The edges of the nodule do not generally taper off into a definite spindle shape. On section the appearance is that of rather large flattened giant cells, somewhat deserving the name of syncytial masses, because of cytoplasmic bridges between them with a rather scant collagenous framework. The cytoplasm is basophilic and the owl-eyed nuclei predominate.

Fibrillar Type

The last stage in the evolution of the Aschoff body before it becomes transformed into an interfascicular scar may properly be referred to as the fibrillar type (Fig. 14). The cells have definitely elongated themselves and approach the characteristics of fibroblasts. The extremely scant and generally still basophilic cytoplasm is arranged as blunt ends situated at either side of the elongated nucleus. The nuclei are now preponderatingly of the fibrocytoid variety, although owl-eyed forms may occur in fair numbers. The incidence of giant cells has become very small, whereas pyknotic nuclei are seen as frequently as in the mosaic types. The collagen has almost completely lost its eosinophilic swollen appearance and is represented by varying amounts of parallel, more or less isolated delicate fibrils with a rare swollen fragment. The argentophilic reticulum has now flattened itself out and from this stage on becomes less and less prominent.

Because of the fibrillar appearance of this Aschoff body type, it may be confused with the reticular Aschoff body. However, it is to be noted that the latter presents a swollen interlacing feltwork of eosinophilic collagen and that the cells are either round with deeply staining nuclei and scant cytoplasm or may appear considerably larger, ovoid, with a generous admixture of the three types of nuclei described. Giant cells may also occur. On the other hand, in the further evolution of the fibrillar Aschoff body, difficulties may be encountered in differentiating it from a somewhat cellular scar. However, the occasional presence of a giant cell and, here and there, of a ragged edge to the cytoplasm or blunt tip to the cell, and the presence of fibrocytoid, owl-eyed and pyknotic nuclei should render this lesion sufficiently characteristic to identify it as an Aschoff body.

Discussion

The purpose of this descriptive classification is two-fold: first, to prepare the ground for further reports in which an effort will be made to ascertain the life cycle of the Aschoff body and to introduce as far as possible a time component into such studies; second, to reduce the controversies on the morphology of the Aschoff body to definite com-

mon denominators by showing that while these lesions occur in a variety of definitely recognizable forms they nevertheless retain each in themselves a sufficient number of characteristic features to justify their consideration as specific of rheumatic fever. The descriptive material in this report, which is largely devoted to separating the Aschoff body into definite categories, at the same time suggests a terminology that should be found useful for future studies. Moreover, this classification possesses sufficient elasticity to permit the addition of suitable descriptive terms (*viz.*, syncytial mosaic Aschoff body, giant cell polarized Aschoff body, and so on). Inasmuch as the lesions falling into these categories represent stages in an evolutionary process, it is to be expected that transitional forms will be encountered. In such cases a hybrid term may be employed. For example, Figure 15 illustrates a lesion that seems to be a transition from a coronal into a mosaic type. It may, therefore, be called a "coronal mosaic" Aschoff body. Figure 16 illustrates a transition between the polarized and fibrillar form and may be properly designated a "polarized fibrillar" Aschoff body.

While the earliest rheumatic lesions, where swelling of the collagen and leukocytic reaction are the only components, can by no means be considered specific of rheumatic fever, the types described in this classification, which represent further stages in the evolution of the lesion, seem to be absolutely specific, differing entirely from the lesions found, for example, in uncomplicated scarlet fever and subacute bacterial endocarditis, or in other inflammatory lesions of the heart. Simultaneously with the studies described here, an investigation was made of the argentophilic reticulum fibers, the cytoplasm, collagen, nuclear characteristics and the giant cells found in other lesions, such as in syphilis, tuberculosis, Hodgkin's disease, foreign body granulomas and Bracht-Wächter lesions, but there never was encountered unusual difficulty in discerning the Aschoff body from the lesions found in the above mentioned conditions.

The most frequently occurring and consistent common denominator in the structure of the Aschoff body is the basophilic cytoplasm with ragged edges. However, no single component can be designated as by itself forming a sufficiently characteristic feature to identify the Aschoff body. On the other hand, the polymorphous basophilic cells with their ragged edges, the swollen and fragmented collagen, the giant cells of the variety described in this report, the varying propor-

tions of somewhat large, owl-eyed, fibrocytoid and pyknotic nuclei, and the argentophilic network, form a sufficiently characteristic group of features to distinguish this lesion from those found in other diseases.

Summary

The clinical histories and anatomical material from 70 cases of uncomplicated rheumatic fever with Aschoff bodies in the myocardium were investigated. A classification of Aschoff bodies is suggested, based on the appearance and distribution of the collagen, argentophilic fibers, cell cytoplasm and nuclei. This classification includes seven types of Aschoff bodies which apparently bear some relation to the life cycles of the lesions. Each type is described and is considered to possess sufficient characteristic features to identify it as an Aschoff body specific of rheumatic fever.

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DESCRIPTION OF PLATE

PLATE 117

FIG. 1. Small cell coronal Aschoff body. A, central swollen mass of collagen; B, cell with owl-eyed nucleus and increased cytoplasm; C, fibrocytoid nucleus. The majority of the cells present scanty cytoplasm.

FIG. 2. Reticular Aschoff body. A, swollen collagen fibers forming interlacing network; B, cell with increased cytoplasm. Note that the collagen framework assumes a direction roughly along the lines of the myocardial bundles. The majority of the cells present scanty cytoplasm.

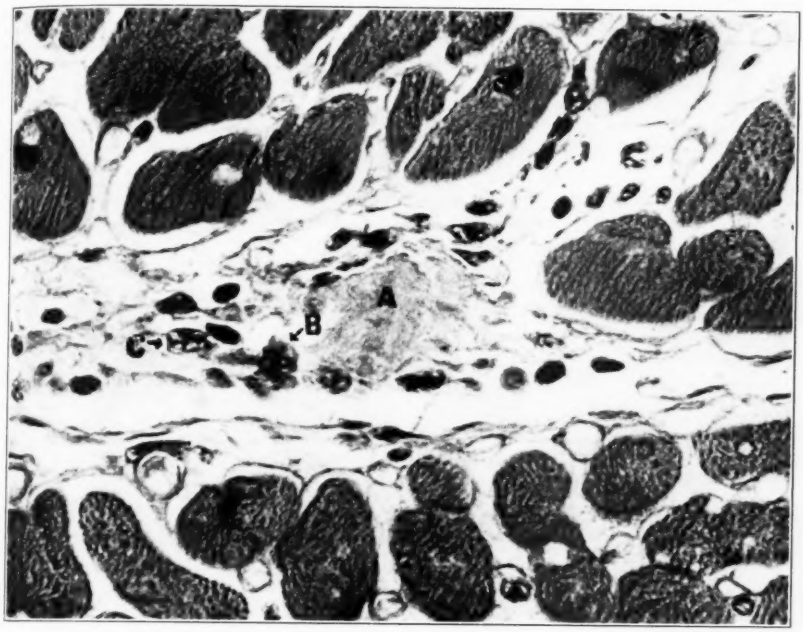

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PLATE 118

FIG. 3. Stage preceding the formation of small cell coronal Aschoff body. A, swollen eosinophilic, somewhat fragmented collagen surrounded by small round cells.

FIG. 4. Large cell coronal Aschoff body. A, central swollen mass of collagen with some fragmentation; B, cell with fibrocytoid nucleus and indistinct cytoplasmic outline; C, cell with owl-eyed nucleus.

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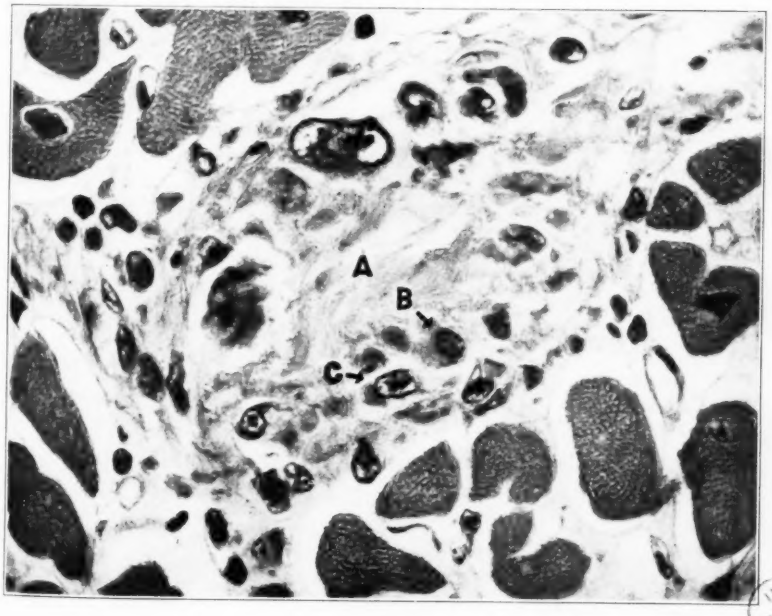

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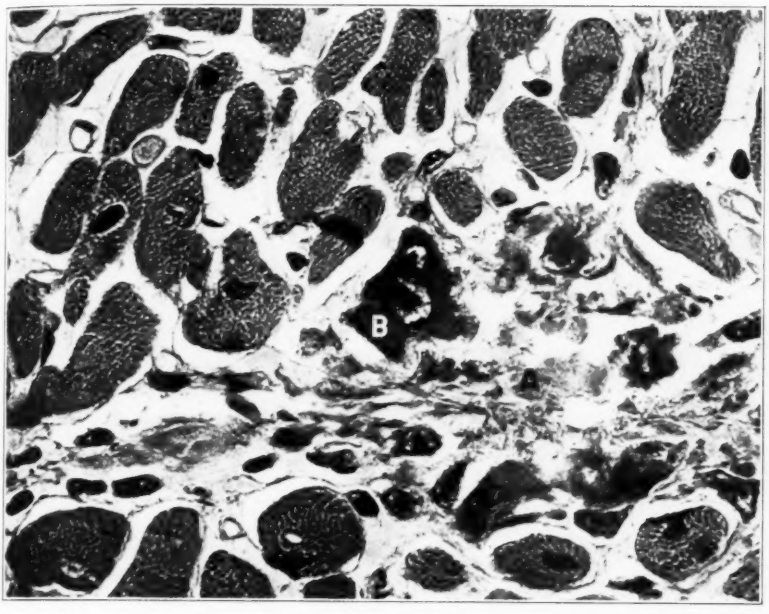
PLATE 119

FIG. 5. Large cell coronal Aschoff body. A, central swollen mass of collagen with some fragmentation; B, giant cell with ragged edges and owl-eyed nuclei. Note the marked basophilia of the cytoplasm (dark staining).

FIG. 6. Syncytial coronal Aschoff body. A, portion of syncytial cytoplasmic mass showing extremely indistinct cellular outline; B, cytoplasmic mass with peripheral location of owl-eyed nuclei; C, masses of swollen collagen. Note small round cells in periphery of Aschoff body.



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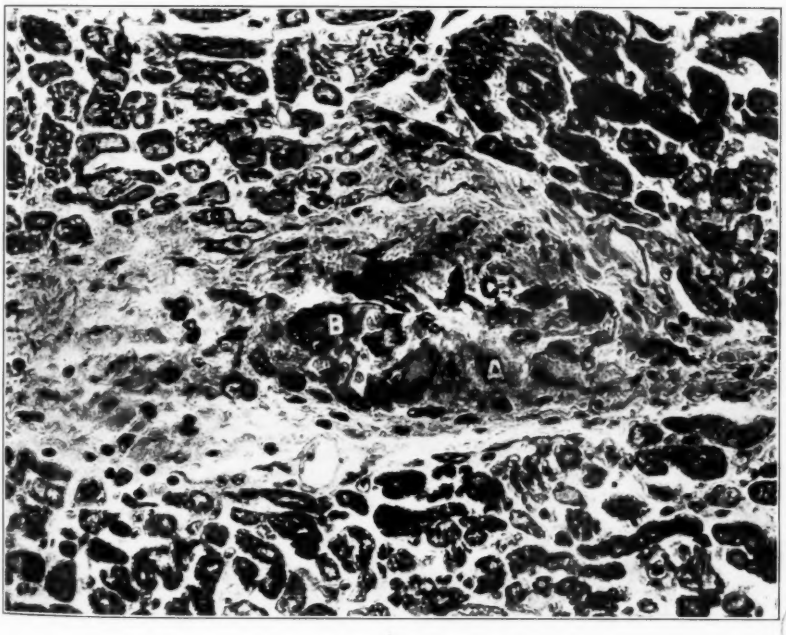

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PLATE 120

FIG. 7. Early stages in the development of the reticular Aschoff body in the form of irregular clumps and tangles. The lesion cannot be considered specific until cellular evolution has reached the formation of owl-eyed, fibrocytoid and pyknotic nuclei with development of cytoplasmic basophilia.

FIG. 8. Reticular Aschoff body showing (A) considerable fusion of collagen fibers.

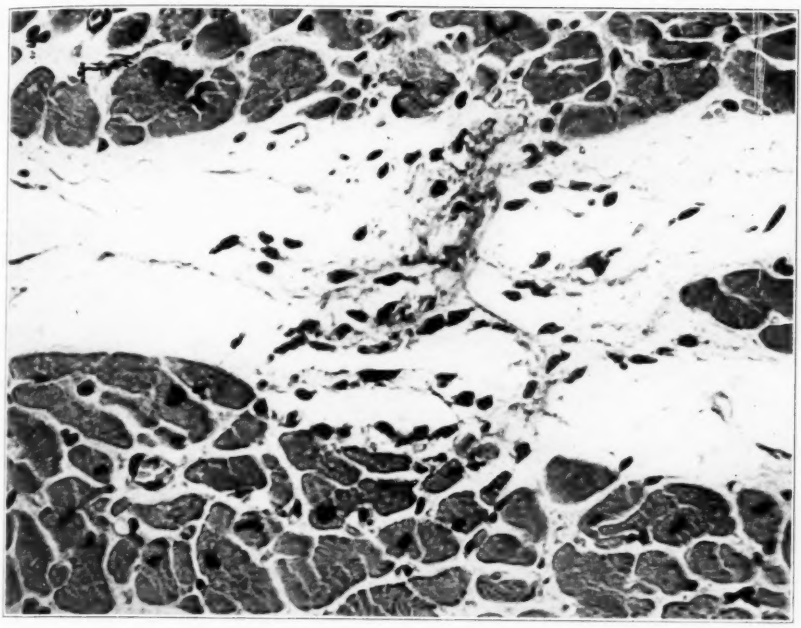

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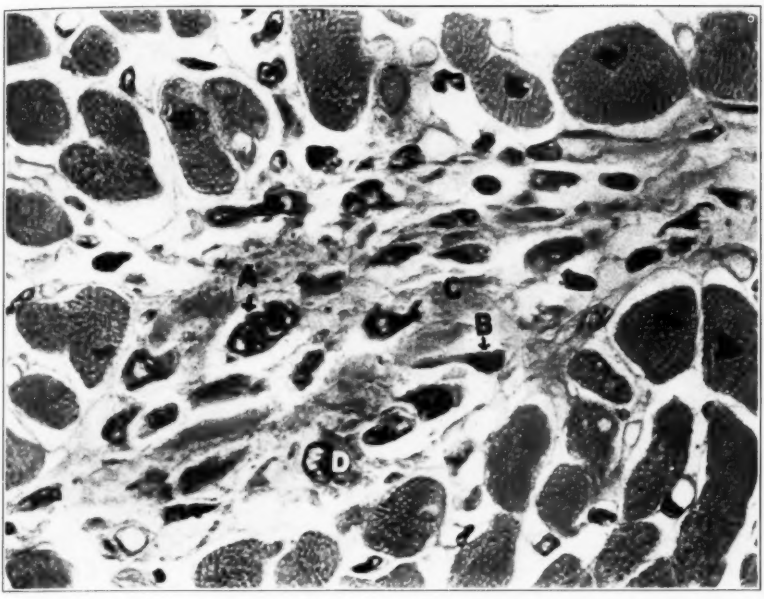
PLATE 121

FIG. 9. Mosaic Aschoff body of the more compact variety. Note the slight polarization of the cells. A, giant cell with irregularly outlined cytoplasm and two owl-eyed nuclei; B, cell with pyknotic nucleus and basophilic cytoplasmic streamer; C, swollen collagen; D, cell with extremely irregular ragged edges.

FIG. 10. Mosaic Aschoff body of looser structure. Note fragmented appearance of collagen. A, fibrocytoid nucleus with radiating bar arrangement of chromatin; B, giant cell with owl-eyed nuclei; C, pyknotic nucleus.



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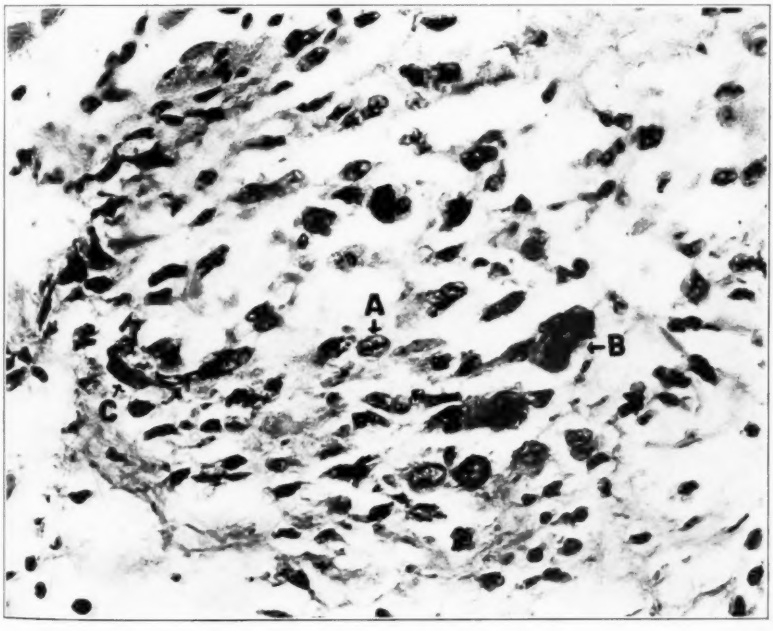

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Plate 122

Fig. 11. Large irregular cell polarized Aschoff body. A, pyknotic nucleus; B, giant cell with owl-eyed nuclei; C, fragment of swollen collagen.

Fig. 12. Polarized Aschoff body showing swollen and fragmented collagen and evolution of cells into spindle types.

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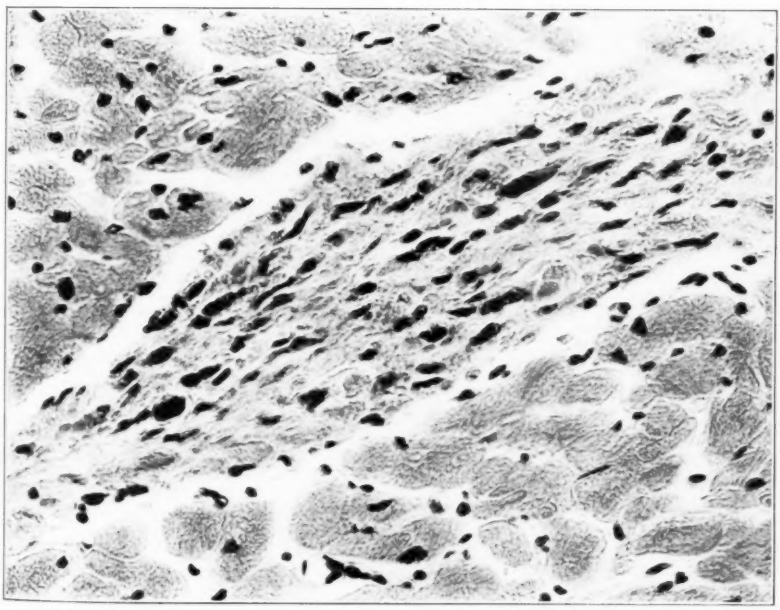

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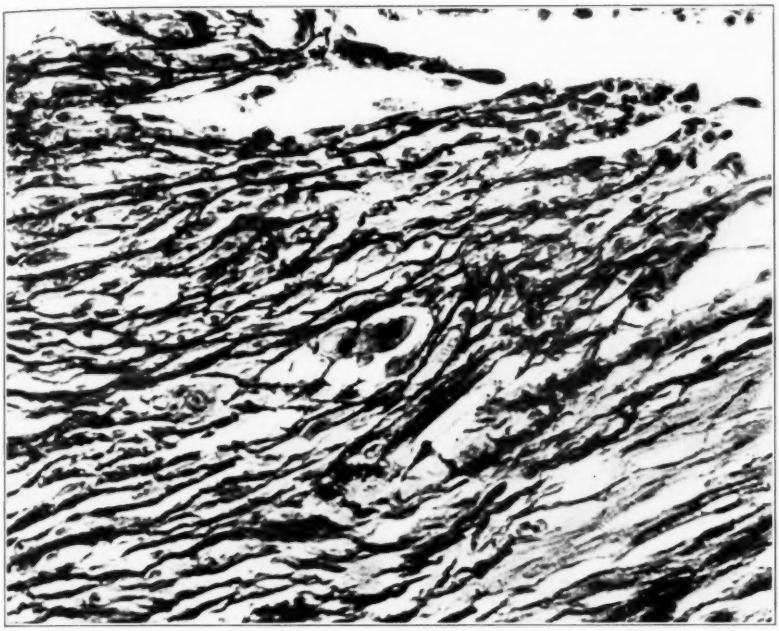
Gross and Ehrlich Studies on the Myocardial Aschoff Body. I

PLATE 123

FIG. 13. Argentophilic reticulum network in polarized Aschoff body.

FIG. 14. Fibrillar Aschoff body. Note the location of this lesion between the muscle bundles. Some of the cells still retain their basophilic cytoplasmic streamers. The nuclei still occur in the owl-eyed, fibrocytoid and pyknotic forms.



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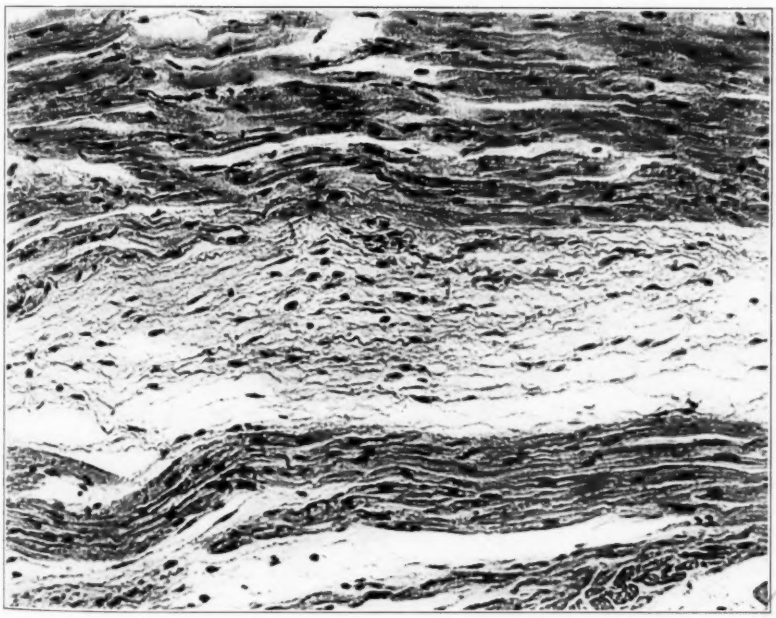

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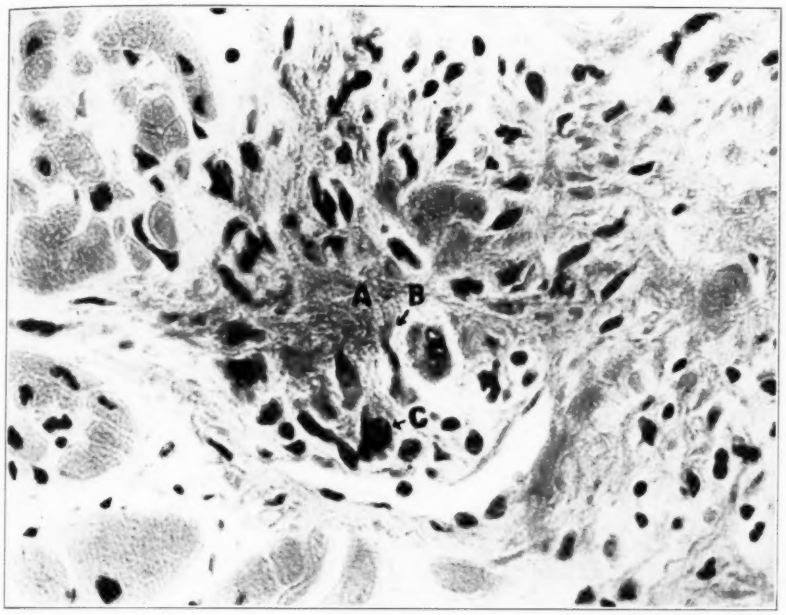
PLATE 124

FIG. 15. Coronal mosaic Aschoff body. A, central swollen collagen; B, cytoplasmic streamer from a cell penetrating the collagenous mass; C, large cell with pyknotic nucleus.

FIG. 16. Polarized fibrillar Aschoff body. Note marked elongation of cells with development of delicate collagen fibers.



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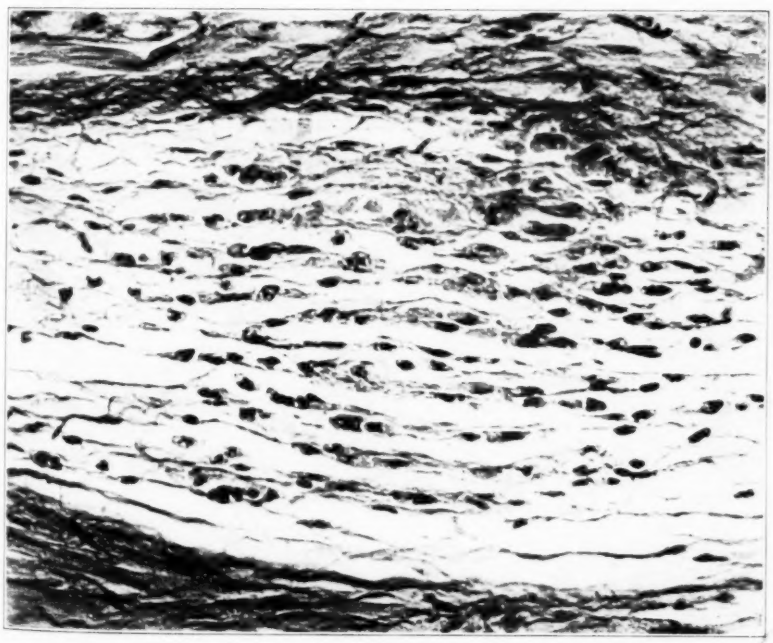

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Gross and Ehrlich Studies on the Myocardial Aschoff Body. I

STUDIES ON THE MYOCARDIAL ASCHOFF BODY *

II. LIFE CYCLE, SITES OF PREDILECTION AND RELATION TO CLINICAL COURSE OF RHEUMATIC FEVER

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This report represents an attempt to throw further light on the nature of the myocardial Aschoff body, its life cycle, sites of predilection, frequency of occurrence, and its possible relation to the clinical course of rheumatic fever. In a previous publication [1] we have shown that the Aschoff body occurring in the heart should be considered apart from the corresponding rheumatic lesions found in other tissues, such as skin, diaphragm, tendinous insertions, and so on, inasmuch as the myocardial lesions present specific characteristics that are either lacking in the other sites or have been insufficiently studied as yet. Furthermore, within the heart proper the Aschoff bodies appear to present characteristics that are definitely influenced by their site. Thus, the subendocardial, left auricular endocardial and perivascular lesions occur in a compressed form which modifies markedly the topography of the evolutionary stages. Within the looser milieu of the interstitial connective tissue between the myocardial bundles the Aschoff body passes through the various stages of its life cycle relatively unhampered by dense fibro-elastic tissue and, accordingly, presents its more characteristic and fully developed metamorphoses. For these reasons the studies presented here will concern the Aschoff bodies situated between the myocardial bundles — lesions that we have referred to as myocardial Aschoff bodies.

Despite reports, particularly in recent years, in which some doubt is expressed concerning the specificity of this lesion in its relation to rheumatic fever, a review of the literature dealing with the development of our knowledge concerning the Aschoff body reveals sufficient evidence to warrant the definite assumption that this lesion does not occur in the myocardium if rheumatic fever, past or present, can

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safely be ruled out of consideration. We shall assume, therefore, for purposes of this study, that it is absolutely specific of this disease.

It is pertinent to this report to mention that one of the reasons for doubting the specificity of this lesion has been the fact that the Aschoff body assumes allegedly protean forms and that one cannot, therefore, speak of a "typical Aschoff body." In a paper presented before the American Association of Bacteriologists and Pathologists [2] we have shown that the supposed protean appearance of the Aschoff body is due to the fact that the published descriptions have not infrequently referred to different stages in the life cycle of the lesion and that, on the contrary, there is a remarkable constancy in the appearance that these inflammatory nodules assume. We have been able to show [1] that each stage in the development of the lesions apparently presents such a uniformity in characteristics that the Aschoff bodies in their specific forms (the earliest stages — collagen swelling and mesenchymal cell proliferation — cannot be considered a specific picture) may be classified into seven relatively clear-cut and easily recognizable types. Occasionally hybrid forms may be encountered, which undoubtedly represent transitions from one type to another. In order that the argument throughout this report may be followed more easily we shall first present a short description of the seven types of Aschoff bodies found in the myocardium. A discussion on the classification of these lesions, together with a fuller demonstration of their histological characteristics, will be found elsewhere.[1]

Abstract of Classification of Aschoff Bodies

1. *Small Cell Coronal Type:* This consists of a central swollen mass of eosinophilic collagen surrounded by round or oval cells somewhat larger than lymphocytes with a delicate mantle of basophilic cytoplasm which presents a sharply defined edge. The nuclei are of the three types that have been described by us as common to all types of Aschoff bodies in which, however, they occur in different proportions: (1) fibrocytoid, (2) owl-eyed, and (3) pyknotic. Giant cells are occasionally seen. This type of Aschoff body shows the beginnings of a network of argentophilic reticulum fibers.

2. *Large Cell Coronal Type:* This differs from the small cell type in the following respects: the cytoplasm is more abundant, the edges

may be diffuse and ragged, giant cells are seen somewhat more frequently and the network of argentophilic fibers is more prominent.

3. *Syncytial Coronal Type:* In this type the giant cells assume the form of large syncytial basophilic masses with ragged edges. These masses arrange themselves around generally small, centrally located fragments of swollen collagen. Owl-eyed nuclei are quite prominent and tend to assume a peripheral situation within the cytoplasmic masses.

4. *Reticular Type:* This consists of a feltwork of interlacing, swollen collagen fibers which frequently fuse at their points of intersection. Within the meshes of this network there are to be found small cells, round or ovoid, with scant basophilic cytoplasm. Occasionally larger cells with a scattering of owl-eyed, fibrocytoid and pyknotic nuclei may be found. Giant cells may be present. Variations occur in this type in which the collagenous meshwork may be extremely irregular, or where fusion may go on to the extent that larger collagenous masses are produced.

5. *Mosaic Type:* This type is characterized by a fairly regular intermingling of cells and collagen. The cells are abundantly cytoplasmic, deeply basophilic, somewhat fragmented and possess ragged edges. The collagen is swollen, eosinophilic and often fragmented. The cells may be squeezed between the crypts of the collagen masses and connected by delicate cytoplasmic streamers, or the mosaic may be of looser structure, in which case the cells tend to be extremely irregular in shape. The argentophilic fibers occur in the form of a net.

6. *Polarized Type:* In this type the cells begin to assume a spindle shape. They may still be somewhat irregular and elongated or they may present a somewhat smoother contour and still retain the basophilia of the cytoplasm. The entire collection of cells takes on a definite direction within the planes of the myocardial bundles. The argentophilic network is somewhat compressed.

7. *Fibrillar Type:* This is a stage that precedes complete metamorphosis of the cells into fibroblasts. As a consequence the cytoplasm is extremely scant, occurring at times as somewhat blunt basophilic knobs at either end of the much attenuated cell. The nuclei are largely fibrocytoid. Giant cells are infrequent. The collagen occurs predominantly in the fibrillar form. The argentophilic fibers are rapidly disappearing.

As to the origin of the cells, we have already stated that it is safest to assume that they arise from mesenchymal elements, understanding by this term an ultimate derivation from the mesenchyme which may or may not have passed through a differentiation into mature cell types such as lymphocytes, histiocytes or fibroblasts. It is also accepted by many observers that injury to the collagen framework of the heart plays the most conspicuous rôle in the determination of these lesions. As a consequence Aschoff bodies occur at those sites where the collagen is found in the greatest amount, *viz.*, in the planes between the myocardial bundles, in the fibro-elastic tissue around blood vessels and in the endocardium. It is the primary lesion to this collagen, with the subsequent development of cellular reaction of a specific type, that gives rise to the Aschoff body.

The first question with which we shall deal is whether a given heart presents a relatively uniform development of Aschoff bodies in respect to their type. Obviously, if this is not the case, any attempt to introduce a time component in the development of the life cycle of this lesion becomes fraught with such difficulty as to make it an apparently hopeless task. Furthermore, such a state of affairs would lend support to the argument that the Aschoff body may arise in a variety of forms. It may be said at once, therefore, that in an examination of 70 hearts possessing Aschoff bodies we have found that a given section usually presents one type of Aschoff body, occasionally two and rarely three. Furthermore, one frequently encounters in the heart a remarkable uniformity in Aschoff body types, particularly if the specimen is obtained from a patient dying in a first attack, or where the attack has taken place a long time (2 years or more) subsequent to a previous attack. This consistency in the structure and, therefore, in the age of the Aschoff body permits of the reasonable assumption that a given crop of lesions may be timed from the onset of a given attack; and since they reach the same evolutionary stages in development, as judged by their appearance at the time of death, it would seem that these lesions pass through an orderly and probably similar series of progressive changes.

Life Cycle of the Aschoff Body

Several of the published reports make mention of the ultimate fate of the cells concerned in the formation of the Aschoff body. Thus, Aschoff,[3] in 1904, believed that the cells eventually transform them-

selves into fibroblasts. Geipel [4] in 1905 observed the development of the lesion in the 5th to 6th week after the onset of the illness, the formation of giant cells and the swelling and later fibrillar change of the ground substance. Takayasu [5] in 1909 described what appears to have been a mosaic Aschoff body occurring 3 months after the onset of the illness. An excellent contribution along these lines was made by Talalajew [6] in 1929, who divided the evolution of the Aschoff body into three phases: (1) exudative, found at the end of the 2nd or during the 3rd week of the illness; (2) proliferative, occurring in the 2nd or during the 3rd month and lasting, at times, 6 months; and (3) sclerotic, appearing during the 2nd month and lasting, at times, 6 months. In 1930 we [2] presented evidence of many evolutionary phases in the development of the Aschoff body through coronal, mosaic, polarized and fibrillar stages. While a sequence of events was suggested, no intimation was made of the actual time component of each phase. Additional information concerning the time it takes to reach the several evolutionary stages of the Aschoff body was formulated by Klinge [7] and his associates in a series of papers (1929 to 1933). According to this work, at the end of the 2nd week of the illness this lesion is represented by swelling of the collagen fibers and increase of connective tissue and wandering cells, with the presence of occasional giant cells. After the 4th week many swollen and multinucleated cells are found arranged either in rosette form around swollen collagen or dispersed throughout it. From this period on involutionary changes take place through the disappearance of the giant cells and "fibrin" and the development of connective tissue cells.

Before proceeding with our own observations on the life cycle of the Aschoff body it may not be amiss to mention the criteria employed by us to determine the sequence of events and the time factors in the cycle. As mentioned before, 70 hearts, each presenting Aschoff bodies in the myocardium, were studied. These were described grossly, particular care being taken to note the extent of valvular damage. The specimens were generally fixed in formol-saline,* and blocks were cut and stained by a number of methods designed to demonstrate changes in the collagen, tinctorial properties of the cytoplasm, details in nuclear structure and presence of

* For a more detailed description of the methods employed see Gross and Ehrlich.[1]

bacteria, fibrin, argyrophilic reticulum and elastic tissue. The case records from all this material were studied in order to determine the clinical course and particularly to set the time of onset of the last attack.

Apart from the clinical records we attempted to fix the onset of the attack by the extent of the valvular damage, as determined by its macroscopic and microscopic appearance and by the histology of the left auricular lesion, when present. The most reliable guide, however, appeared to be the state of the collagen. In common with a number of observers we were impressed with the fact that the collagen was the first to show damage in the form of swelling and the assumption of eosinophilic properties. The earliest appearance of swelling was, therefore, taken as confirmatory evidence that we were dealing with the beginning of the cycle. In this stage (early phases) the reticular and small cell coronal Aschoff body type predominated. On the other hand, it seemed equally reasonable to assume that the late phases of the cycle were associated with the appearance of fibroblasts (metamorphosis of the Aschoff cells) and the transformation of the swollen collagen into the delicate fibrillar form. These stages were associated with the polarized and fibrillar forms of Aschoff bodies. Moreover, the clinical records confirmed the fact that these were late stages in the evolution of the attack. There remained, therefore, the large cell coronal, syncytial coronal and mosaic forms which, both by the nature of the collagen and on structural considerations, appeared to fall naturally in between these extremes in the age of their development (middle phases). At best, of course, these can be considered no more than an approximation to what actually happens in the human heart.

The material least subject to criticism on which it is permissible to attempt the reconstruction of the stages through which the Aschoff body passes is represented by cases where the individual died in his first attack, and where the time of onset of the disease is definitely known. For this purpose we had available 9 cases, all children who died from 2 to 13 weeks after the onset of the rheumatic fever symptoms, *e.g.*, joint pains and temperature. It is to be noted that in a discussion of the time component of these lesions we shall date their age from the onset of the rheumatic phenomena — disregarding what may be considered a prodromal period, namely, the possible preceding attack of sore throat, scarlet fever, and so on. It

is generally believed that this prodromal period may vary from several days to 4 to 5 weeks. A study of these "first attack" cases indicates that the earliest lesions are of the reticular type, and that fibrillar forms are not found by the end of the 13th week, at least in the limited number of cases available for study. On the other hand, a careful selection of material from cases where the individual suffered from more than one attack presents clear-cut evidence that in these clinical groups the initial lesions may be represented by reticular, as well as small cell coronal forms. Furthermore, an opportunity is thus made available to study the development and time factors of the fibrillar form.

As indicated in a previous publication, it seems fairly certain that the earliest stages consist of swelling, eosinophilic metamorphosis and a certain amount of fusion of the collagen fibers with, *pari passu*, proliferation of the mesenchymal elements. These non-specific early stages may occur in two forms which eventually develop into the coronal and reticular Aschoff body types.

Before entering into a description of the sequence of events that represent the life cycle of the Aschoff body it is of value to classify our material into four clinical groups representing the course taken by the rheumatic fever process in our 70 cases which came to autopsy and presented Aschoff bodies in the myocardium. This classification was undertaken because it appeared that the clinical course of the disease modifies to a certain extent the evolutionary process of the Aschoff body in a given case.

Clinical Classification of Rheumatic Fever Material

Group 1. Cases where the individual died in a first attack.

Group 2. Cases where one attack occurred prior to the final fatal recurrence.

Group 3. Repeated attacks with death during an acute recurrence.

Group 4. Cases where death was caused by decompensation without clinical evidence of a final recurrence. Some of these cases had no previous history of rheumatic fever.

Early Phases: In the "first attack" cases (Group 1), as well as in the other groups where the collagen in the interstices of the myo-

cardium exists in a somewhat loose fibrillar form, the reticular Aschoff body apparently represents the earliest specific lesion. In addition, however, in Groups 2, 3 and 4 the early lesion is also represented with about the same frequency by the small cell coronal Aschoff body type, both types existing side by side in the same blocks taken from the myocardium. The fact that the Group 1 cases show reticular forms exclusively (or, perhaps, predominantly) suggests that the form taken by the initial lesion is apparently influenced not only by the fact that the small cell coronal form begins around more compact collagen, but possibly also by the altered reactivity of the individual, due to the fact that he has already suffered an initial attack. These early stages (early phases) are found in from 2 to 4 weeks after the onset of the disease. Since we did not have any cases where the individual died sooner than 2 weeks after the onset of the disease we have been unable to determine precisely how soon the earliest specific lesion may be found before this time.

Middle Phases: Depending upon whether the earliest lesion is the reticular or small cell coronal Aschoff body type, the nodule may develop in one of two main directions during its middle phase. The reticular form rapidly shows increase in the size of the cells, during which time the collagen may either become more delicate, or fuse and undergo granular degeneration. If the collagen becomes relatively inconspicuous and delicate the cells elongate themselves and there develops the picture of the large irregular cell polarized type. If the collagen undergoes fusion and granular degeneration the resultant picture may be one indistinguishable from the mosaic type with necrotic collagen. This process apparently takes place between the 4th and 13th week after the onset of the illness.

The small cell coronal Aschoff body transforms itself into the large cell variety by swelling of the cell cytoplasm. These swollen cells soon appear to penetrate into the collagenous central mass and eventually permeate it in such a manner as to form the mosaic Aschoff body. If the intercellular collagen undergoes granular degeneration a picture is produced that simulates the corresponding form already described as derived from the reticular Aschoff body. The stage during which the cells begin to permeate the central collagenous mass can be referred to as the coronal mosaic Aschoff body. In some cases the cells of the large cell coronal Aschoff body undergo amitotic division, fusion and enormous enlargement, form-

ing huge syncytial masses which surround the relatively insignificant collagenous central portion (syncytial coronal Aschoff body). This lesion was found most frequently in the "first attack" group and generally appeared during the 9th week after the onset of the attack. Eventually, the syncytial masses disintegrate and produce a picture indistinguishable from the mosaic forms. As in the development that takes place from the reticular Aschoff body, these middle phases in the evolution from the small cell coronal lesion also occur between the 4th and 13th week after the onset of the disease.

Late Phases: The large irregular cell polarized Aschoff body, as well as the mosaic Aschoff body, whether derived from the reticular or small cell coronal lesion, now begins to show elongation of the cells to spindle forms. The cytoplasm still retains its basophilia but the outlines become sharp. The collagen becomes scanty and there is thus developed the polarized Aschoff body. Apparently, these lesions generally appear from the 9th to the 16th week after the onset of the disease. It is seen, therefore, that no matter which of the two initial lesions subsequently develops through the evolutionary stages of the Aschoff body, the lines of development apparently ultimately converge into the polarized forms.

From this point on, the spindle cells apparently transform themselves into fibroblasts. Delicate collagenous fibrils, which may ultimately fuse into dense collagenous bundles, appear between the cells. For some considerable time, however, the cells still retain rather blunt basophilic knobs of cytoplasm at either end of the elongated nucleus. Furthermore, whereas giant cells become extremely scarce and the nuclei become largely fibrocytoid, there are still to be seen a sufficient admixture of owl-eyed and pyknotic nuclei which, together with the peculiarity of the cells, distinguish this lesion as specific of rheumatic fever. We have designated these lesions as fibrillar Aschoff bodies. They apparently occur some time after the 13th week following the onset of the illness. The final stage in the evolution of this specific inflammatory lesion is the complete metamorphosis of the fibrillar Aschoff body into scar tissue which lies rather characteristically between the muscle bundles.

Figure 1 illustrates diagrammatically the lines of development of the Aschoff body, starting from the reticular and small cell coronal lesions and ending in the fibrillar type. An indication is given of the time component, although it must be realized that the attempt which

we have made at timing the development of these lesions represents an average arrived at from a study of relatively few specimens. There can be no doubt that considerable variations occur in the tempo, but this can be determined only from a much larger series of cases.

Relation of Aschoff Body Type to Clinical Course of Rheumatic Fever

In examining the types of Aschoff bodies found in the four clinical subdivisions of rheumatic fever outlined above several observations seemed to be worthy of note. Thus, the small cell coronal lesion was not found in the first group. This may have been due to the limited material available. On the other hand, as stated before, it may represent a difference in the reactivity of these "first attack" cases from the other clinical types. The large cell coronal, syncytial coronal and mosaic types were found more frequently in this group than in the other three. Fibrillar forms were not found. This may be due to the fact that death occurred within 13 weeks after the onset of the illness in the cases that comprised this group. In the second clinical group the incidence of small cell coronal and fibrillar types, as the initial lesions, was about equal. Mosaic forms occurred frequently, perhaps, however, slightly less often than in the first group. Fibrillar forms occurred with moderate frequency and large cell coronal types were relatively infrequent. The third group showed a further decrease in the incidence of mosaic forms, the lowest incidence of fibrillar forms found in any group with the exception of Group 1, and the highest incidence of polarized forms found in any group. Inasmuch as these two types of lesions are to a certain extent reciprocals of one another this observation does not indicate a fundamental difference in this group. No reticular forms were found in the fourth group, which otherwise showed approximately the same incidence of lesions as found in the second group. The conspicuous points in these observations appear to be the absence of small cell and fibrillar Aschoff bodies in Group 1, the high incidence of mosaic forms and the relatively high incidence of large cell coronal and syncytial coronal forms in this group, and the absence of reticular lesions in Group 4.

Incidence and Distribution of Aschoff Bodies in the Myocardium

The figures quoted in the earlier literature (see Clawson [10]) on the incidence of Aschoff bodies in the hearts of patients dying from rheumatic fever are considerably higher than those obtained by later investigators. The reason for this discrepancy undoubtedly lies in the fact that the earlier workers chose active cases on which to make their studies. On the other hand, the figures recently published have also been high, probably because of better recognition of these lesions and a more thorough search for them. In comparing the reported incidence it must be remembered that the type of material studied plays an important rôle. Unless the proportion of acute and chronic cases studied is indicated no true comparison can be made. Furthermore, as will be shown later, the number of blocks studied and, more particularly, the sites from which these blocks have been taken, will materially influence the results obtained. Of the more recently published figures it is of interest to note that Aschoff bodies were found in the myocardium in 18 of Libman's [8] 56 cases (32 per cent), 20 of Kugel and Epstein's [9] 24 cases (83 per cent), 31 of Clawson's [10] 50 cases (62 per cent), 24 of McClenahan and Paul's [11] 28 cases (85.7 per cent), 42 of Gross, Antopol and Sacks' [12] 79 acute and chronic cases (53 per cent), and in 60 of Thayer's [13] 64 cases (93.7 per cent).

In our present statistics, which are based on a study of the standardized blocks, Aschoff bodies were found in approximately 59 per cent of 161 hearts showing evidence of rheumatic infection, past or present, and in 90 per cent of hearts in cases that showed evidence of activity, clinically or pathologically. The clinical evidence of activity can be considered to consist of joint pains, choreic manifestations and fever. The anatomical evidences of activity consist of fresh verrucous lesions, fresh pericarditis and acute inflammatory phenomena in the myocardium, valve rings and valve leaflets. The question of the relation of activity to myocardial failure and the incidence of these phenomena during the first eight decades of life have been studied by Rothschild, Kugel and Gross,[14] who were able to show that during the first five decades of life myocardial failure is closely paralleled by activity in the myocardium.

Classifying our rheumatic material that presented Aschoff bodies in the myocardium into the four groups outlined above, we observed

that in the first group ("first attack" cases) myocardial Aschoff bodies are almost invariably found in the interventricular septum (T.V.*) and in the upper part of the posterior wall of the left ventricle (M.P.). The posterior wall (myocardium) of the left auricle (L.A.), left posterior papillary muscle (P.P.M.) and pulmonary conus (P.A.V.) show the presence of Aschoff bodies in about 60 per cent of the cases. The myocardial wedge between the aorta and left auricle (A.M.V.) shows Aschoff bodies in only a small percentage of the cases.

The Group 2 cases, *i. e.*, those where the individual suffered from one previous attack, show a decidedly lower incidence of auricular myocardial Aschoff bodies (approximately 20 per cent), but the same incidence of lesions in the upper part of the posterior wall of the left ventricle (M.P.). The distribution of Aschoff bodies in the other sections is similar to that in Group 1, but approximately 15 per cent lower in incidence. In Groups 3 and 4 myocardial Aschoff bodies were not found in the myocardial wedge between the aorta and left auricle (A.M.V.). They were rare in the posterior wall of the left auricle (L.A.). The distribution of Aschoff bodies in the left posterior papillary muscle (P.P.M.), the interventricular septum (T.V.) and pulmonary conus (P.A.V.) was in the same proportion as the corresponding sites in Group 1, but about 30 per cent lower in incidence. In Group 3 Aschoff bodies were found in the upper part of the posterior wall of the left ventricle (M.P.) in 90 per cent of the cases, in Group 4 in 64 per cent of the cases. Perivascular and subendocardial Aschoff bodies, on the other hand, in contrast to what we have termed "myocardial Aschoff bodies," seem to occur with greater frequency in Group 4 cases.

In summarizing our findings in these four groups it seems that when Aschoff bodies are found in all the standardized blocks the case almost invariably falls into the first group of our clinical classification. Furthermore, involvement of the myocardium of the posterior wall of the left auricle (L.A.) with Aschoff bodies occurs almost as frequently as it does in the posterior wall of the left ventricle (M.P.) and interventricular septum (T.V.). Conversely, the left auricular myocardium (L.A.) is seldom involved with Aschoff bodies in the remaining three groups. The incidence of Aschoff bodies in the up-

* These bracketed initials refer to the abbreviated terminology employed by Gross, Antopol and Sacks [12] to designate the standardized sections.

per part of the posterior wall of the left ventricle (M.P.) remains approximately the same (90 per cent) in the first three groups. It is somewhat lower in the fourth group. The incidence of Aschoff bodies in the interventricular septum (T.V.) is extremely high (almost 100 per cent) in the first group. It varies from 66 per cent to 88 per cent in this site in the remaining groups. This curious rearrangement in the incidence of Aschoff bodies in various parts of the heart, brought about by the clinical course of the disease, again suggests the possibility of some alteration in the reactivity of the tissues induced by the nature and frequency of previous attacks.

Quite apart from this clinical grouping of our material, it may be stated that when Aschoff bodies are present in the myocardium they will be found almost invariably either in the interventricular septum (T.V.) or posterior wall of the left ventricle (M.P.). The next most frequent sites in the order of frequency with which Aschoff bodies are found are the left posterior papillary muscle (P.P.M.), pulmonary conus (P.V.), posterior wall of the left auricle (L.A.) and myocardial wedge between the aorta and left auricle (A.M.V.).

Discussion and Summary

There has been presented in this report a study of the life cycle of the myocardial Aschoff body, based on an examination of the clinical records and autopsy material from 70 cases that presented Aschoff bodies in the myocardium. It appears that these specific lesions pass through three stages in development. The earliest phases, represented by small cell coronal and reticular Aschoff bodies, have been found to occur up to the 4th week after the onset of the illness. The middle phases, represented by large cell coronal, syncytial coronal, mosaic and large irregular cell polarized Aschoff bodies, have been found to occur between the 4th and 13th week after the onset of the illness. The late phases are represented by polarized Aschoff bodies which occur from the 9th to the 16th week after the onset of the illness, and subsequently by fibrillar Aschoff bodies which occur after the 13th week of the illness.

The earliest types of specific lesions are apparently influenced in their response by the reactivity of the tissue, depending on whether there has or has not been a previous attack of rheumatic fever, and also by the state of the collagen present in the interstices between the

myocardial bundles. As a consequence, the evolution of the lesion may follow one of two main courses, determined by the initial lesion. The latter may occur in the form of the reticular or the small cell coronal Aschoff body. The final phases of the life cycle of the Aschoff body are common to both main courses.

Dividing the material into four groups representing different clinical courses, there appears to be some change both in the incidence of the types of Aschoff bodies present in the myocardium and in their localization. The findings reported here, however, can by no means be considered as furnishing sufficient statistical evidence on which to base final conclusions on this point. That the tempo of the life cycle may be considerably faster or slower than what has been described in this report seems very probable. Some of the stages in the "model" of the life cycle presented by us may be absent in some cases, abbreviated in others, or indeed, appear in the reverse order from what we have suggested. These facts can be determined with greater accuracy only after examining a much more extensive series of cases and, in the last analysis, must await confirmation by the hitherto unsuccessful transmission of this disease to animals. It is hoped, however, that further studies will be made along these lines in order that some of these interesting relations may be placed on a firmer footing.

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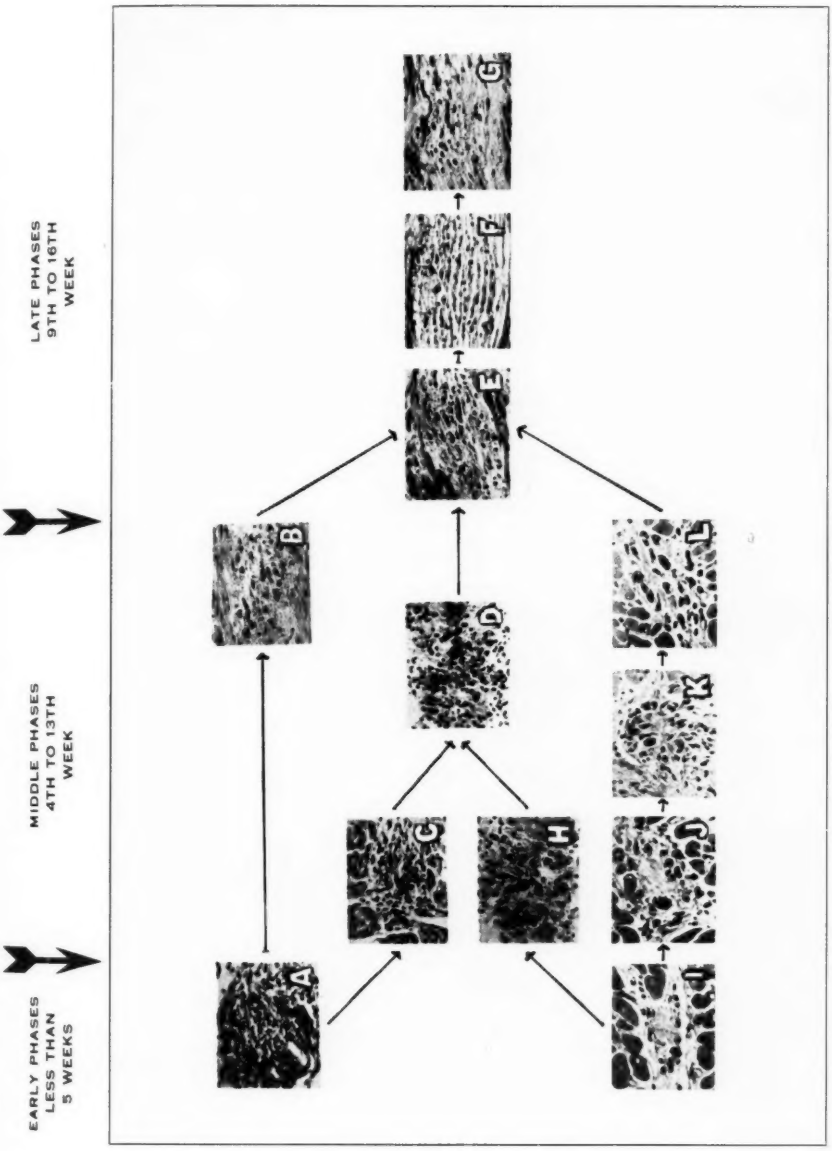
DESCRIPTION OF PLATE

PLATE 125

FIG. 1. Aschoff body types illustrating various stages in the life cycle of the lesion. A, reticular stage; B, large irregular cell polarized stage; C, reticular stage with fusion and granular degeneration of collagen fibers; D, mosaic stage with granular degeneration of collagen; E, polarized stage showing marked spindle cell formation; F, polarized fibrillar stage; G, fibrillar stage; H, large cell coronal stage with granular degeneration of collagen; I, small cell coronal stage; J, large cell coronal stage; K, coronal mosaic stage; L, mosaic stage, compact form with beginning polarization.


LATE PHASES
9TH TO 16TH
WEEK
MIDDLE PHASES
4TH TO 13TH
WEEK
EARLY PHASES
LESS THAN
5 WEEKS
A
B
C
D
E
F
G
H
I
J
K
L

THE DISAPPEARANCE OF GLOMERULI IN CHRONIC KIDNEY DISEASE *

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It is a common opinion that the ultimate fate of a glomerulus damaged beyond recovery is cicatrization and atrophy with the formation of a more or less permanent spherical hyaline scar. Experimental evidence, however, is lacking to determine whether such scars are permanent, or whether they eventually disappear. The ratio between intact and scarred glomeruli has been believed to furnish some indication of the amount of renal parenchymatous destruction. An estimate derived from such observations of the extent of renal damage would be justified if the glomerular scars were permanent, but if they were to disappear without trace the final histological picture would give less insight into the amount of damage, and even the pathogenesis of the disease, than is commonly supposed. Investigators of the pathological histology of Bright's disease have recognized tubular atrophy and disappearance since the time of Cohnheim,[1] but as indicated in a recent review by Fahr,[2] and in the even more recent histological studies of McGregor [3] and of Oliver and Lund,[4] the obliterated glomerulus has not been followed beyond the spherical hyaline scar. Both MacCallum [5] and Mosenthal [6] mention the possibility of complete glomerular disappearance. Joelson, Beck and Moritz [7] in a study of dog kidneys at varying intervals after temporary ureteral obstruction inferred that glomeruli may completely disappear without leaving recognizable scars, providing sufficient time were allowed to elapse between injury and examination.

If the spherical hyaline scars in a diseased kidney are permanent monuments to destroyed nephrons their number plus the number of non-contracted glomeruli should equal the number of glomeruli found in a normal kidney. To investigate this the number of patent glomeruli in a kidney has been estimated by the injection method,

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and the proportion of injected and uninjected glomeruli and glomerular scars determined by examination of histological sections. From these observations the total number of intact and scarred glomeruli in a given kidney could be calculated.

Determination of Patent Glomeruli by Injection

The number of patent glomeruli was estimated by Kunkel's [8] modification of Vimtrup's method. Human and rabbit kidneys were obtained as soon after death as possible, usually within 12 hours in the former and immediately in the latter, were weighed, and cannulae tied into the renal artery and vein. The kidney was then perfused at 140 mm. Hg. pressure with a mixture of equal parts of 2.5 per cent potassium ferrocyanide and ferric ammonium citrate after the blood had been completely washed out with physiological salt solution. It was then stripped of all fat, including that in the pelvis, weighed again and four blocks taken for histological sections. These were also weighed. By weighing the fat that had been removed the original weight of the kidney before perfusion was obtained. The kidney was cut into pieces, macerated in 50 per cent HCl for 24 to 36 hours, and then transferred to water in which the maceration was continued for 24 to 48 hours. By this time the kidney was quite soft and could easily be drawn through a tube 2 mm. inside diameter. The macerated kidney was then diluted to a suitable volume, thoroughly mixed, and the glomeruli in 2 cc. aliquots counted on a ruled Syracuse watch glass under a binocular biobjective microscope. Glomeruli are resistant to digestion and appear as deeply stained blue balls amid pieces of broken tubules. Twenty aliquots from at least three samples of the final dilution were counted.

Histological Examination

The blocks taken for histological sections were fixed in acidified formalin, washed, dehydrated and embedded in paraffin in the usual manner. Sections were cut 6 microns thick at intervals of 0.1 mm. from each block and were stained either with hematoxylin and eosin or by the Van Gieson technique. The percentage of injected glomeruli, non-injected but apparently patent glomeruli, and glomerular scars was determined by differential count. Scars of

doubtful identity were counted as glomeruli, so that any error in the differential count represented more glomeruli than were actually present rather than less. This procedure gave added significance to estimated totals which were less than the expected normal. The estimation of the total glomeruli by injection and the differential counts in sections were made independently by different observers.

In making calculations it was assumed that the distribution of patent and obliterated glomeruli throughout the kidney was fairly uniform. The histological examination of blocks taken from different parts of the kidney seems to justify this assumption.

From these data two calculations were made: first, from the proportion of apparently patent but uninjected glomeruli the total number of possibly patent glomeruli was estimated; and second, from the proportion of fibrous and apparently patent glomeruli the total number of recognizable glomerular structures was calculated. There is probably an error in these estimations since a glomerulus often appeared patent but uninjected in a single section, although serial sections showed that its afferent artery was completely occluded so that it could not be injected. This, however, does not affect the comparison of the total number of glomeruli in the diseased kidney with the normal. An example of calculation follows:

Autopsy No. 4553, Jan. 11, 1934. Weight of kidney and fat before perfusion 275 gm. Weight of kidney after perfusion 226 gm. Weight of blocks for sections 2 gm. Weight of fat 110 gm. Corrected weight of kidney 165 gm. Kidney cut into small pieces and these placed in 50 per cent HCl. January 12, transferred from acid to water. January 13, diluted to 16 liters. Counts on 2 cc. samples: 174, 216, 190, 161, 176, 182, 170, 175, 166, 179, 149, 163, 160, 154. Mean 170.2 ± 12.27. By Fisher's [9] formula $t = 39.13$ and is significant. Estimate of injected glomeruli $170.2 \times 8 = 1361.6$ thousand. Correction for blocks taken for histological section 12 thousand. Corrected estimate of injected glomeruli 1374 thousand. Differential count of 795 glomeruli showed 98 per cent injected, 1.5 per cent apparently patent but uninjected and 0.5 per cent hyaline scars. Correcting the estimate from injected glomeruli gave 1395 thousand apparently patent, and 1402 thousand recognizable glomerular structures.

Normal Kidneys

Estimations of the number of glomeruli in the human kidney have varied tremendously — from 560 thousand to 5,700 thousand by different observers and using diverse methods. By injection of iron salts and acid digestion Vimtrup [10] found 834 thousand to 1,233 thousand, Moore [11] 600 thousand to 1,200 thousand, Hayman and Johnston [12] 800 thousand to 1,500 thousand. The number of glomeruli in the two kidneys of the same animal have been found approximately equal (within 10 per cent) by Hayman and Starr [13] for the rabbit and by Moore for man.

Fourteen kidneys from human subjects between 1 month and 88 years of age were injected (Table I). None had evidence of kidney disease during life, with the exception of 3 who died from acute mercuric chloride poisoning. These have been included in the normal group because of the absence of history of previous kidney disease, the lack of histological evidence of glomerular damage and the fact that a bichloride kidney may be perfused and injected as a normal one.

Of interest in this series was the observation that in a kidney from an infant 1 month of age, 10 per cent of the glomeruli were immature, non-patent structures. This confirms previous observations that postnatal maturation of glomeruli occurs in animals (cats).[14] When these immature glomeruli were included in the total estimate of glomerular structures the number was equal to that found in the adult. Even in "normal" kidneys of young individuals a small number of fibrous or hyaline glomerular scars were found. This number tends to increase slightly with age, but an advanced age may be reached without any significant decrease in the total number of glomeruli. This is at variance with the observations of Moore who found that the number of glomeruli is reduced after the sixth decade. As would be expected, kidneys of very different weights may contain approximately the same number of glomeruli.

The range of the estimations of total glomerular structures in these fourteen kidneys was from 940 to 1542 thousand. The mean was 1,282.8 ± 32.7 thousand and the standard deviation 174 thousand. If a normal distribution be assumed in this sample of 14 kidneys (and there is nothing to indicate that the distribution is not normal), then glomerular counts differing from the mean by more than twice

the standard deviation, or below 933.7 thousand, may represent a significant reduction, while the chances are about 370 to 1 that any count differing by more than three times the standard deviation, or below 759.1 thousand, represents a true reduction. The mean of the present series differs slightly from that found by Hayman and Johnston in a series of 12 normal kidneys, but in which no correction

TABLE I

Glomerular Counts of Normal Kidneys

Autopsy No.	Sex	Age	Kidney weight	Injected glomeruli in macerated kidney	Differential count in sections				Total possibly patent	Total glomerular structures
					Number counted	Injected	Uninjected non-contracted	Fibrous		
			gm.	*thousands*		*per cent*	*per cent*	*per cent*	*thousands*	*thousands*
4480	M	1 hr.	14	1050	1520	89.0	11.0*	..	1180	1180
4495	F	1 mo.	9	944	479	90.0	10.0*	..	1049	1049
4300	F	20 yrs.	115	1004	675	92.0	7.0	1.0	1080	1091
4527	M	20 "	132	1421	781	100.0	..	..	1421	1421
4575	F	21 "	124	1242	701	99.2	0.8	..	1252	1252
4154	F	23 "	156	1230	708	96.2	1.2	2.6	1245	1279
4457	M	28 "	187	1465	548	95.0	4.8	0.2	1438	1542
4372	M	41 "	230	1300	969	99.0	0.6	0.4	1307	1312
4204	M	49 "	268	1238	974	95.5	2.0	2.5	1163	1196
4216	M	51 "	210	1530	869	99.4	0.2	0.4	1533	1539
4553	F	56 "	165	1373	795	98.0	1.5	0.5	1394	1401
A9211	M	65 "	145	905	636	96.3	0.4	3.3	909	940
4337	M	71 "	170	1023	610	85.5	0.7	13.8	1031	1190
4554	M	88 "	114	1298	739	89.0	8.0	3.0	1414	1458

* Immature non-patent glomeruli.

was made for fibrotic glomeruli. The difference in the means (1156 ± 38.8 and 1283 ± 32.6) is 127 ± 61.4 thousand, and is not statistically significant.

CHRONIC RENAL DISEASE

The abnormal kidneys have been grouped according to the type of pathological process (Table II). In these the number of obviously and possibly patent glomeruli has been recorded, as well as the total number of recognizable glomerular structures. The difference between the total possibly patent and the normal number of glomeruli indicates the reduction in the number of functioning units,

or units that may possibly be capable of any function, while the difference between the last figure and the normal measures the number of glomeruli that have disappeared so that they are no longer recognizable. Both of these estimates are probably too high, since any glomerulus that contains dye at all is counted as injected, although many of its capillaries were frequently occluded. The number of possibly patent glomeruli cannot, therefore, be taken as a measure of the extent of the filtering surface. The second figure is probably high also, because it was frequently impossible to distinguish whether an acellular hyaline scar represented an obliterated glomerulus or blood vessel.

In all groups there are instances in which there is not only a significant but even a striking reduction. This is most marked in the cases of diffuse glomerular nephritis. In the arteriosclerotic group there is a significant reduction, not only in the number of patent glomeruli, but also in the total number of recognizable glomerular structures, both in those who died of cardiac failure and in those in whom the arteriolar nephrosclerosis was an incidental autopsy finding. In two of the three patients with vascular disease who died in uremia with renal failure the renal damage had progressed rapidly. In one (4204) clinical evidence of renal impairment had been present for only a month before death, while in another (4147) it had been present less than 6 months. It is probable that in these cases death occurred before the functionless glomeruli had been hyalinized or had disappeared. In the microscopic sections from these kidneys great difficulty was frequently experienced in distinguishing patent uninjected glomeruli from non-patent but not hyalinized glomeruli, so that the count of injected glomeruli is probably a closer estimate of the number of possible functioning structures than the corrected estimate.

It would appear from these data that more than half of all the glomeruli in a kidney damaged by vascular disease or chronic inflammation may disappear without leaving recognizable scars. Furthermore, the disappearance of renal parenchyma, as indicated by the number of remaining glomeruli and glomerular scars, need not be paralleled by a corresponding reduction from the expected normal weight of the kidney.

TABLE II

Glomerular Counts of Pathological Kidneys

Autopsy No.	Sex	Age	Kidney weight	Injected glomeruli in macerated kidney	Differential count in sections				Total possibly patent	Total glomerular structures	Pathological diagnosis
					Number counted	Injected	Uninjected non-contracted*	Fibrous†			
		yrs.	*gm.*	*thousands*		*per cent*	*per cent*	*per cent*	*thousands*	*thousands*	
4147	M	41	150	220	623	37	8	55	269	595	Arteriolar nephrosclerosis
4204	F	48	94	543	612	60	10	30	634	905	Death due to renal insufficiency
4160	M	44	100	222	1015	32	31	37	437	693	
4359	M	41	212	705	993	66	19	15	908	1068	Death due to cardiac failure
4165	M	85	97	467	1123	83	11	6	529	563	
4152	F	38	109	241	808	42	45	13	499	574	
4145	M	67	140	330	1017	60	9	31	378	550	
A9127	F	67	141	734	549	89	1	10	740	824	
4530	F	45	111	386	741	42	20	38	570	919	Death due to cerebral hemorrhage
4172	F	67	83	391	531	93	2	5	399	420	Incidental autopsy finding
4563	F	72	109	663	526	83	4	13	695	799	
A9160	M	46	63	430	927	93	1	6	434	462	
4173	F	52	135	619	720	97	1	2	625	638	
4319	F	49	156	301	508	57	21	22	412	528	Chronic diffuse glomerular nephritis
4274	F	27	72	132	441	43	12	45	169	307	
4557	F	55	39	93	432	35	3	62	101	266	
A9167	F	43	34	127	762	82	3	15	132	155	
4137	F	60	130	771	756	96	2	2	787	803	Chronic pyelonephritis
4139	M	75	170	850	784	95	1	4	859	895	
4485	M	55	118	485	703	95	3	2	501	511	
4200	M	21	163	1119	1086	97	2	1	1142	1154	Focal glomerular nephritis

* It was frequently impossible to determine whether non-contracted, non-dye-containing glomeruli were potentially patent or not.

† It was frequently impossible to determine whether an acellular, hyaline scar represented an obliterated glomerulus or blood vessel. Such scars were counted as glomeruli and probably exaggerate the estimated total number of glomeruli.

The Morphological Aspects of Glomerular Disappearance

If this evidence be accepted as indicating that glomeruli disappear without trace, the histogenesis of this process demands study. For this purpose two uninterrupted series of 200 sections, each 6 microns in thickness, were cut; one from a kidney the seat of nephrosclerosis and the other from a kidney the seat of chronic diffuse glomerulonephritis. The sections from these two series were stained with hematoxylin and eosin, Masson's trichrome light green, Mallory-Heidenhain azan carmine, and Foot's silver carbonate, in rotation, so that the various structural characteristics of a given glomerulus could be observed in adjacent sections. In a number of instances it seemed advisable to study the various elements of a glomerulus in the same section. To do this a glomerulus was photographed repeatedly at a constant magnification, destaining and staining by a different technique between each photograph. In addition to the stains mentioned above, Mallory's phosphotungstic acid hematoxylin was found especially useful for the identification of collagen and fibroglia. Glomerular scars in kidneys the seat of chronic pyelonephritis and hydronephrosis were also studied in this manner.

Normal and diseased glomeruli have recently been described in detail by McGregor, who did not, however, study the components of the glomerular scar. This spherical hyaline body, when stained with hematoxylin and eosin or azan carmine, is apparently of too simple a structure to justify further investigation. Regardless of whether the glomerular damage was the result of arteriolar nephrosclerosis, chronic diffuse glomerular nephritis, chronic pyelonephritis or hydronephrosis, the final spherical hyaline glomerular scars are for the most part indistinguishable from one another. Even after the glomerulus has been converted into a structure which in hematoxylin and eosin preparations appears to be a homogeneous, acidophilic sphere, special stains (azan carmine, phosphotungstic acid hematoxylin) may disclose the shadowy outlines of the wrinkled, thickened basement membrane of arteriolar nephrosclerosis (Fig. 1 B) or the more fibrillar peripheral remnant of a capsular crescent denoting inflammatory change. These distinguishing features are subsequently lost with complete hyalinization (Fig. 2 B).

Four fibrillar elements are concerned in the organization and disappearance of the glomerular scar in chronic renal disease. The only stainable intercellular structure normally present in a glomerulus is the basement membrane of the tuft. This membrane is covered by epithelium and lined by endothelium and is in structural continuity with the capsular and tubular membranes (Fig. 4 A). Furthermore, it stains in the same manner except that it is not argentophilic, whereas the membrane surrounding capsule and tubule has an argentophilic component (Fig. 4 B). In nephrosclerosis the argentophobic glomerular and the argentophobic portions of capsular and tubular basement membranes are thickened, but the argentophilic component is not altered, the accretion of substance being inside of it (Figs. 1 B and 1 C). With contraction and hyalinization of the glomerular scar the more or less continuous argentophilic capsular membrane becomes disrupted and there is irregular prolongation of the interstitial silver staining fibrils into the periphery of the hyaline mass (Fig. 2 C). Argentophilic fibrils also appear at the vascular hilum and develop in the center of the scar. The original argentophobic tuft membrane has in the meantime lost its identity and has become incorporated in the hyaline mass. The scar gradually loses its spherical contour, is rendered irregular by superficial concave defects, and within it there are focal areas of rarefaction (Fig. 3 B). The penetrating peripheral and central argentophilic fibers become confluent and conform in pattern to that of the interstitial tissue of the kidney, and the last recognizable trace of the glomerulus is a local collection of small, irregularly outlined, confluent hyaline bodies lying in the interstices of an argentophilic mesh.

The other two fibrillar elements are collagen and fibroglia. Collagen fibrils appear only in the peripheral portion of the glomerular scar and are not seen in the more advanced examples of organization. Their situation would suggest that they are derived from the capsular fibrous tissue. Fibroglial processes develop within the substance of the hyaline sphere and do not appear to play any important part in its organization. The probable source of these processes is from capillary endothelial cells that survive within the scar. These cells enlarge, elongate, and come to resemble fibroblasts. No example of a completely acellular scar was encountered and no evidence of fibroblastic penetration of the scar was recognized.

Fatty degeneration of the scar occurs especially in kidneys the

seat of rapidly progressive disease. The degeneration is frequently severe enough to leave large defects in the otherwise hyaline mass. In the less rapidly progressive types of renal disease fatty degeneration is inconspicuous. Calcification is occasionally present in the form of finely dispersed granular deposits, but is rarely extensive.

The Disappearance of Glomeruli Following Experimental Renal Injury in Rabbits

Various attempts were made to produce unilateral renal injury of sufficient severity to effect a certain amount of diffuse irreparable glomerular damage, so that the total number of surviving glomerular

Table III

Glomerular Counts of Rabbits' Kidneys

Rabbit No.	Left (control) kidney				Right (injured) kidney				Type injury	Recovery period
	Injected glomeruli in macerated kidney	Differential count		Total glomerular structures	Injected glomeruli in macerated kidney	Differential count		Total glomerular structures		
		Injected	Uninjected and scars			Injected	Uninjected and scars			
	thous'ds	*per cent*	*per cent*	*thous'ds*	*thous'ds*	*per cent*	*per cent*	*thous'ds*		*days*
101	167	98	2	170	137	98	2	140	X-ray	27
102	144	97	3	149	115	89	11	130		63
131	163	99	1	165	146	98	2	149		71
133	181	98	2	185	122	94	6	130		71
134	183	99	1	185	126	88	12	143		71
132	179	99	1	181	130	99	1	132		77
130	140	97	3	144	33	88	12	39		153
143	116	100	..	116	89	90	10	99	Ureter kinked	56
144	99	98	2	101	36	99	1	37		56
145	166	98	2	169	96	94	6	102		56
2842	128	100	..	128	120	98	2	123	Vein clamped 17 hrs.	90
148	178	100	..	178	179	100	..	179	Control	

structures could be compared with the number of glomeruli in the other (normal) kidney. Of the methods tried, temporary partial ureteral obstruction and exposure to X-ray proved most satisfactory in our hands. For unilateral injury by X-ray the kidney was delivered through a lumbar incision, the animal protected with lead foil,

and the exposed kidney subjected to from 2 to 5 human erythema doses. Partial ureteral obstruction was produced by kinking the ureter just above the bladder by suturing in to the latter. After 35 days the animal's abdomen was again opened, the sutures cut and the ureter straightened. At this operation the ureter was found to be dilated, while at autopsy this had disappeared.

As indicated in Table III, complete disappearance of as many as 70 per cent of all the glomeruli in a rabbit's kidney may occur without the persistence of scars to denote their previous existence. This lends confirmation to the suggestion previously made by Joelson, Beck and Moritz regarding glomerular disappearance in the dog.

Discussion

It has been shown that both in chronic renal disease in man and in experimentally produced glomerular injury in rabbits a large proportion of the glomeruli in a given kidney may disappear, leaving no recognizable trace. In the case of the rabbits, where the disease was not progressive, there was not even any condensation of the interstitial connective tissue to indicate the loss of parenchyma. In man the chronic progressive nature of the disease made interstitial fibrosis a constant finding, even though the recognizable glomerular scars were not numerous enough to account for more than a fraction of the obliterated glomeruli. The reduction of the number of glomeruli was not paralleled by a corresponding reduction from the expected normal weight of the kidney.

If so large a proportion of the glomeruli in chronic renal disease can disappear without trace, as is indicated in Table II, the final histological examination of the kidney may give less information concerning the pathogenesis and severity of the disease than is commonly thought. If a kidney, having originally an expected normal number of about one million glomeruli, can lose as many as three-fourths of these without leaving recognizable scars of those lost, it is not fair to assume that the changes affecting the one-fourth remaining were necessarily the same as those that occurred in the glomeruli that have disappeared. The final pathological diagnosis of the kidney is frequently made on a basis of the preponderant change seen. This may involve a weighing of the evidence of arteriolar sclerosis against the evidence of inflammation. If complete

glomerular disappearance occurs to the extent indicated in this investigation the final pathological picture may throw but little light on the pathogenesis of certain types of chronic renal disease.

Summary and Conclusions

1. The number of possibly patent glomeruli and glomerular scars has been estimated by a combination of injection and histological methods.

2. The average number of glomeruli in 14 normal human kidneys was 1,282.8 ± 32.7 thousand.

3. In chronic renal disease not only the number of patent glomeruli but the total number of recognizable glomerular structures was reduced. This was most marked in chronic glomerular nephritis. The number of possibly patent glomeruli frequently falls below 500 thousand and may be below 200 thousand. The total number of recognizable glomerular structures, including scars, was frequently below 600 thousand and in some instances below 300 thousand.

4. Since large numbers of glomeruli may disappear during the course of chronic renal disease it is suggested that the final histological pattern may not give as much information concerning the pathogenesis or severity of the disease as is commonly thought.

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DESCRIPTION OF PLATES

PLATE 126

FIG. 1 A, B and C. Three photographs of the same section including a glomerular scar in an early stage of organization.

A, stained by hematoxylin and eosin.

B, stained by the Mallory-Heidenhain azan carmine method.

C, stained by Foot's silver carbonate method. × 300.

In A the spherical hyaline scar appears quite homogeneous. In B the denser staining, thickened basement membrane of the tuft can be identified. In C the argentophilic capsular membrane is quite intact, but in the center of the scar reticulum fibrils, continuous in serial sections with the vascular hilum, may be seen.

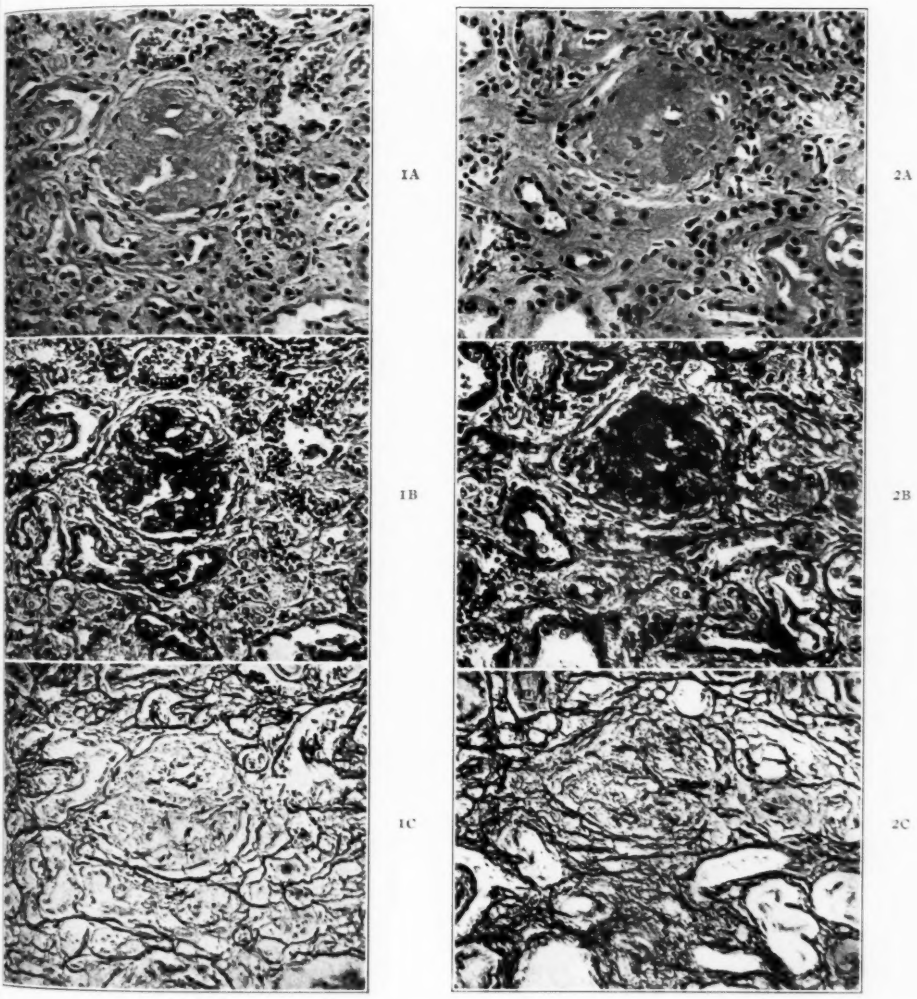
FIG. 2 A, B and C. Three photographs of the same section including a glomerular scar which shows more advanced organization than is seen in Fig. 1.

A, stained by hematoxylin and eosin.

B, stained by the Mallory-Heidenhain azan carmine method.

C, stained by Foot's silver carbonate method.

In both A and B the scar appears homogeneous but in C the capsular reticulum is discontinuous and the scar shows peripheral penetration from the interstitial tissue and central penetration from the vascular hilum by argentophilic fibrils. × 300.



Moritz and Hayman Disappearance of Glomeruli

PLATE 127

FIG. 3 A and B. Two photographs of the same section cut through the middle of the almost completely absorbed glomerular scar.

A, stained by hematoxylin and eosin.

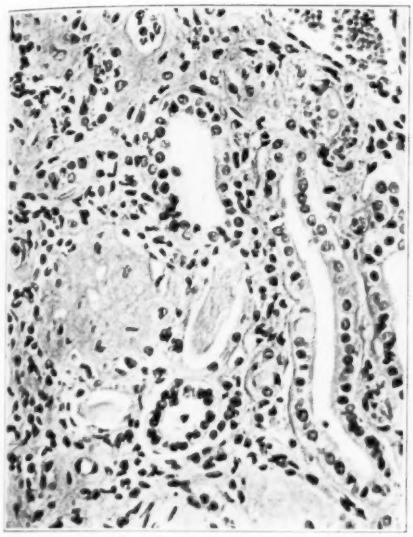
B, stained by Mallory-Heidenhain azan carmine method.

In A the scar appears to be homogeneous and spherical. In B the scar is seen to be irregularly absorbed from within and from without. A comparison of the distribution of nuclei in A with the distribution of the areas of hyaline absorption in B indicates that the disappearance of hyaline occurs around cells that appear to be fibroblasts. × 385.

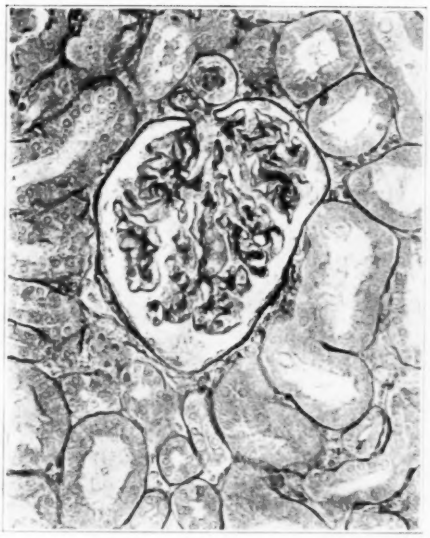
FIG. 4 A and B. Two photographs of normal glomeruli.

A, glomerulus stained by the Mallory-Heidenhain azan carmine method to show the continuity of the capsule (and tubular) basement membrane with that of the tuft. × 385.

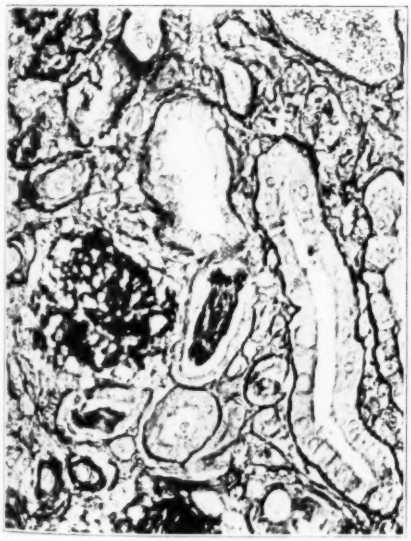
B, glomerulus stained by Foot's silver carbonate method to show that the argentophilic component of the capsular and tubular membrane is not continued into the basement membrane of the tuft. × 385.



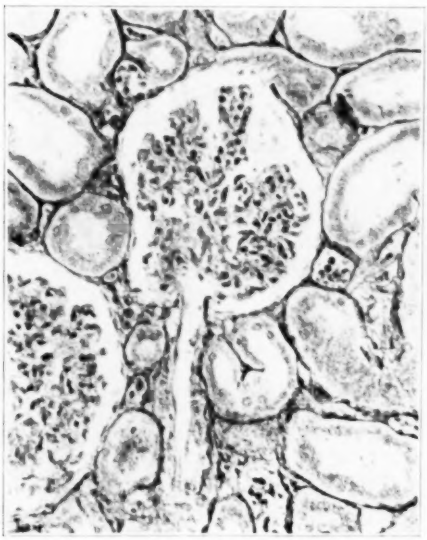
3A



4A



3B



4B

Moritz and Hayman

Disappearance of Glomeruli

ACTINOMYCOSIS OF TUBES AND OVARIES *

REPORT OF A CASE

V. H. CORNELL, M.D.

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The table and bibliography appended hereto have been made as comprehensive as possible in an attempt to collect in the English literature all cases of actinomycosis of the internal female genitalia. There have been found 71 published cases,† some of which are listed as parametrial and perhaps should not be included. The American literature records 7 cases, the English 6 and the remainder are in other languages. Of the 71 cases 45 died, in 7 the outcome is not recorded, 8 were improved and only 11 cures are claimed or inferred. Of the 11 cures only 2, those of Martin and Martius, are reported as exceeding 1 year. Both patients were well, over 3 years after discharge. It has been learned in a personal communication that Brickner's patient, who had been well for 2 years when reported in 1924, died in 1930 of actinomycosis.

Helwig, Brickner, and Draper and Studdiford give good reviews of relatively recent date in English, and Nürnberger's chapter on the subject is excellent in German. These articles give reviews of current opinions as to etiology, diagnosis and treatment. The intestinal tract is possibly the primary site of infection, and extension is generally by continuity of tissue. Early operative intervention, potassium iodide, Roentgen therapy and possibly yatren appear to be the treatments of choice. These facts appear generally agreed upon.

* Received for publication November 27, 1933.

† One additional case has been indexed since submitting the above article for publication. Rumpf, E. Geschlossene Ovarialaktinomykose. *Zentralbl. f. Gynäk.*, 1933, **57**, 1216–1218. This case occurred in a female 40 years of age, whose appendix was removed in May, 1929, at which time the internal genitalia appeared only slightly injected. In September of that year she was taken suddenly ill, a mass was found in the left pelvis and this grew to the navel. Puncture drainage by vagina was followed by temporary improvement. In May, 1930, severe symptoms returned and laparotomy was performed July 21, 1930. Bilateral ovarian and parametrial involvement by actinomycotic abscesses was found. Death occurred 5 days after operation from peritonitis.

TABLE I

Published Cases of Actinomycosis of Internal Female Genitalia

No.	Author	Date of publication	Age	Location	Treatment	Duration	Result
			yrs.				
1	Zemann [1]	1883	30	Parametrium	Not given	17 mos.	Died
2	Zemann [1]	1883	40	Right tube	Not given	1½ mos.	Died
3	Zemann [1]	1883	50	Left ovary	Not given	6 mos.	Died
4	Middeldorpf	1884	32	Ovary	Symptomatic	15 mos.	Died
5	Illich	1892	?	Parametrium	Operation	4 mos.	Died
6	Samter [2]	1892	36	Parametrium	Operation	4 mos.	Died
7	Samter [2]	1892	35	Parametrium	Operations	15 mos.	Died [3]
8	Samter [2]	1892	26	Left ovary	Operations (drainage)	3¼ yrs.	Died
9	Redtenbacher	1893	19	Uterus and adnexa	Operation (drainage)	14 mos.	Died
10	Stewart and Muir	1893	35	Ovaries and right tube	Not given	10½ mos.	Died
11	Giordano	1895	64	Uterus	Operation and zinc chloride	4 yrs.	Cured (?)
12	Habel	1896	45	Right ovary	Puncture (drainage)	5 wks. (?) [4]	Died
13	Litten	1900	39	Right ovary	Not given	1 yr.	Died
14	Fehmers	1901	?	Parametrium	Operation (dr.) and KI	2½ yrs.	Died
15	Fehmers	1901	?	Parametrium	Operation (dr.) and KI	8 mos.	Died
16	Hart	1902	49	Parametrium and left ovary	Operation	5½ mos.	Died
17	Henriot	1902	21	Left adnexa	Operation	17 mos.	?
18	Geldner	1903	15	Ovaries	Operation	1 yr.	Died
19	Rosenstein	1904	17	Right ovary	Operation and KI	4¾ yrs.	Cured (10 mos.)
20	Verocay	1905	14	Uterus and adnexa	Symptomatic	5 mos.	Died
21	Zwintz	1905	41	Parametrium and adnexa	Puncture (dr.) and iodin	18 mos.	Died
22	Litten and Levy	1906	44	Tubes	Symptomatic	?	Died
23	Schlagenhaufer	1906	38	Right ovary	Operation (dr.) and KI	22 mos.	Died
24	Schlagenhaufer	1906	19	Right tube and left ovary	Operation (drainage)	9½ mos.	Died
25	Hamm	1906	39	Tubes	Operation	13 yrs. (?)	?
26	Martin	1906	?	Parametrium	Operation (dr.) and iodine	2¼ yrs.	Cured (?) [5]
27	Neuhauser	1907	60	Uterus and right ovary	Operation	19 mos.	Died
28	Guicciardi	1907	18	Parametrium	Operation (drainage)	3 mos.	Improved
29	Thompson	1907	?	Left ovary	Operation	2 yrs.	Died
30	McMorrow	1908	?	Parametrium	Operation (drainage)	3½ mos.	Died
31	Hamm and Keller	1909	34	Uterus and adnexa	Operation	6¾ yrs.	Died
32	Taylor and Fisher	1909	34	Right ovary	Operation and KI	4¾ yrs.	Improved
33	Leith	1909	?	Ovary and tube	?	?	?
34	Bondy	1910	28	Right and left adnexa	Operation (dr.) and KI	11 mos.	Died
35	Wagner	1910	19	Right and left adnexa	Operation, KI, copper [6]	7 yrs.	Cured (?)
36	Shaw	1910	38	Parametrium and left ovary	Operation [7]	11 mos.	Died

Published Cases of Actinomycosis of Internal Female Genitalia (Continued)

Published Cases of Actinomycosis of Internal Female Genitalia (Continued)

37	Wätjen	1911	?	Right ovary	Operation [8]	2–7 yrs.	?
38	Toennies	1911	21	Right ovary	Operation	3½ mos.	Died
39	Hedinger	1913	40	Tubes	Operation	?	?
40	Wunschik	1913	38	Ovaries	Operation, KI, arsenic	5½ yrs.	Cured (5 mos.)
41	Kohler	1914	33	Left ovary	Operation	7 mos.	Died
42	Robinson	1919	15	Right and left adnexa [9]	Operations	8½ mos.	Cured (4 mos.)
43	Brandenstein	1920	13	Right tube	Operation	8 mos.	Cured (?)
44	Schröder	1922	29	Ovaries	Operation	3 mos.	Died
45	Hüffer	1922	40	Uterus and right ovary	Operation	10 wks.	Improved
46	Schmidt	1924	45	Right ovary and tube	Operation and KI	4 mos.	Died
47	Mitra	1924	49	Rt. tube and ovary, par., cervix	Operation	9 mos. (?)	Died
48	Nürnberger	1924	38	Right tube and ovary	Operation, KI, X-ray	?	Died
49	Christeller	1924	49	Cervix	?	(Short)	Died
50	Helwig	1925	26	Right tube and ovary	Operation	4 yrs.	?
51	Brickner [10]	1925	18	Right ovary	Operations	11½ yrs.	Died (8 yrs. later)
52	Horalek	1925	?	Right and left adnexa	Operation, X-ray	5½ mos.	Cured (10 mos.)
53	Draper, Studdiford	1926	36	Left ovary and right tube	Operations [11]	8 mos.	Died
54	Bax	1927	32	Tubes and left ovary	Drainage and KI	22 mos.	Died
55	Fischer	1927	?	Ovary	?	?	?
56	Stein	1928	39	Right and left adnexa	Operations	6½ mos.	Died
57	Haselhorst	1928	20	Uterus, adnexa, parametrium	X-ray, iodin	10 mos.	Died
58	Barth	1928	46	Uterus, left tube, parametrium	X-ray, KI, yatren, drainage	18 mos.	Died
59	Perazzi	1928	21	Parametrium	Drainage	1 mo.	Died
60	Faust	1928	28	Left ovary (and right ?)	Operation, KI, X-ray	3 mos.	Improved
61	Faust	1928	54	Right ovary, parametrium	Operation, omnadin	3 yrs. (?)	Died
62	Ahlstrom	1930	45	Right and left adnexa	Operation, X-ray, KI	11 mos.	Died
63	Martius	1930	54	Left ovary	Operation, X-ray, KI, yatren and radium [12]	11 mos.	Cured (3 yrs.)
64	Schugt	1930	24	Right and left adnexa	KI, X-ray	1 yr.	Cured (?)
65	Sprengell	1930	23	Tubes	Operation	14 mos.	Improved
66	Bloch	1931	21	Parametrium	Drainage, X-ray, KI, yatren	3¼ yrs.	Died
67	Fátyol	1931	32	Right tube and ovary	Operation, KI	1½ yrs.	Cured (4 wks.)
68	Boys	1932	36	Left tube and ovary	Operation, KI	4½ mos.	Died
69	Ikeda and Ikeda	1932	37	Parametrium	Drainage, KI, radium	5 mos.	Improved
70	Heim	1932	21	Right ovary (and tubes ?)	Operation	?	Improved
71	Klingen	1933	31	Right ovary	Operation, KI, enemas, yatren, X-ray	10 mos.	Improved

1. Cases 1, 4 and 5, respectively, of Zemann.
2. Cases 15, 16 and 19, respectively, of Samter.
3. Death recorded at beginning of report.
4. Appendectomy 6 years previously.
5. Martin's case published in 1906: states therein that since fall of 1902 recovery was complete, a 3 or 4 year cure.
6. Copper sulphate used in 1:100 dilution for irrigation; large doses of potassium iodide.
7. Appendiceal abscess 10 months previously.
8. Appendicitis 7 years previously and appendectomy 2 years previously.
9. Robinson states in this paper that only 19 cases had been reported to date of proved genital organ infection.
10. Died about 8 years later of actinomycosis (personal communication). Received X-ray and radium emanations and sodium and potassium iodides.
11. Records involvement of mesenteric lymph nodes at autopsy and invites attention to fact that only 1 previous case (Brickner's) showed lymphatic involvement.
12. Seen 3 years and 1 month after operation and considered cured.

The following case is reported chiefly because of the cure in 4 years. The history is rather long but interesting and hence included somewhat in detail; it would indicate approximately 10 years duration of infection prior to operation.

Report of Case

J. A. B., a white, female, aged 31 years, was admitted to the Letterman General Hospital, May 3, 1929.

Previous History: The patient was born in European Russia in 1897 and lived at her birthplace until 1917. She was married in 1913, separated from her husband during the World War (1914–1918) and divorced in 1918 without resuming marital relations. Between 1913 and 1919 she had several attacks of "malaria," the diagnosis being clinical only, but the attacks were relieved by quinine. She also had frequent "colds" as a schoolgirl, each of few days duration. She has been more or less constipated all her life. In 1918 she went to Omsk, Siberia, and in 1919 to Vladivostok, where she remained until 1922. In 1919 at Vladivostok she spent 35 days in the City Hospital with severe pain in the right lower quadrant of the abdomen, being treated by vaginal douches and ice externally. In 1919 she met her present husband and has accompanied him since. From 1922 to 1923 she was in Shanghai, suffering from occasional pains in the right lower quadrant, these being at times sharp, as if pulling. They had no relation to menses. From 1923 to 1925 was spent in the Philippine Islands. According to her statement she was twice in the Sternberg General Hospital, Manila, P. I.

History from Sternberg General Hospital: Admitted Aug. 9, 1924, with a history of "ovarian trouble" for 3 years, severe hypochondriac pain for 2 months and acute exacerbation the day prior to admission. No nausea, vomiting or constipation. Weight 148 pounds (normal). Tenderness over McBurney's point. Appendectomy August 10th. The appendix was closely adherent and posterior to the cecum. Urine showed a few pus cells. Feces showed segments of tapeworm. Blood: leukocytes 6800 with 64 per cent neutrophilic polymorphonuclears on August 11th. Wassermann negative. The patient was up in a wheelchair August 22nd (12 days postoperative) and was discharged from the hospital August 31st.

Vaginal smear, on October 3rd was reported positive for pus and Gram-negative intracellular and extracellular diplococci.

Readmitted to Sternberg General Hospital Jan. 6, 1925. This history records dengue fever in July, 1924, some dysmenorrhea and leukorrhea, tapeworm, and pain in region of right ovary. Weight 155 pounds. Tenderness present in both ovarian regions; no masses palpable. Tenia solium removed by vermifuge. Cyst of right Bartholin's gland incised January 16th. Cervical discharge contained pus and a few Gram-positive bacilli. Urine and blood negative. Discharge from cyst of Bartholin's gland contained pus and intracellular Gram-negative diplococci. Cervical smear on January 17th showed no pus but endothelial cells with included bacteria. Operative scar reported non-adherent. Discharged Jan. 22, 1925. (No histological examination of appendix recorded; inquiry in 1929 failed to discover any retained tissue.)

Letterman General Hospital History: The patient stated that the abscess of the labium had existed for 5 years and dates the vaginal discharge as beginning after appendectomy in 1924. Continual use of a pad was required, being renewed daily. She also stated that the pain in the right lower quadrant was much worse after the appendectomy. In 1925 she started for the United States on a naval transport but while at Shanghai went to a Polish doctor who said she should have immediate treatment to prevent cancer. For 3 months he treated her by daily applications to or into the cervix, followed by tamponage, with some dark medicament, and daily douches before each visit to his office; menstruation stopped during this treatment for a period of 4 months. From Shanghai she came to San Francisco, where she has resided since except for 3 or 4 months spent in San Diego in 1925. In San Francisco she was at first treated three times a week by a private physician who used tamponage and douches. There was no improvement or change in the pain during either of these courses of treatment. Then followed treatment for 6 months at a San Francisco hospital, where X-ray was used for diagnosis and the patient informed that her trouble was due to adhesions. She was given a diet and oral medication, losing about 36 pounds during these 6 months (168–132). She was then sent to Letterman General Hospital by a naval surgeon.

Obstetrical History: Menses began at 15 years, were regular and of the 21 day type, 4 to 5 days heavy flow but no pain. The only interruptions have been in 1914, when she became pregnant but miscarried at 3½ months; in 1920, when she again miscarried at 3 months; and in 1925 as recorded. The patient emphatically denies any intervention during either pregnancy.

Present Illness: Admitted May 3, 1929, as an emergency case. She had been vomiting green material for 18 hours, according to her husband's statement, with severe pain across the lower abdomen. She had had a small bowel movement the day of admission and one the previous day. There was always tenderness in the suprapubic region and she had had numerous previous attacks of pain, but none so severe. The pain was chiefly across the lower abdomen, with epigastric distress.

Physical Examination: Pulse 102, temperature 99.2° F, respirations 24. Pulse regular and of good quality. General condition fair. Blood pressure 110/80. Positive findings: moderate leukorrhea; cervix elongated, especially the anterior lip; uterine fundus enlarged and irregular on posterior surface; moderate resistance in both adnexa but examination unsatisfactory because of pain on pressure upward from vagina or upon abdominal pressure; abdomen moderately distended; liver not enlarged; spleen not palpable; marked tenderness over lower abdomen, especially in suprapubic region; no definite muscle rigidity.

Progress and Laboratory Findings:

May 3rd: White blood cell count 15,850, polymorphonuclears 83 per cent at 4:30 P.M. Passed gas and had bowel movement. Urine showed trace of albumin, many pus and epithelial cells. Feces showed undigested food.

May 4th: White blood cell count 8100, polymorphonuclears 65 per cent.

May 5th: White blood cell count 4900, polymorphonuclears 68 per cent. Urine showed a few pus and blood cells.

May 6th: Blood Wassermann negative.

May 7th: On pelvic examination the external genitalia were negative, but there was a slight leukorrheal discharge in the vagina. The cervical canal was patulous with a plug of stringy mucus present; no erosions or cysts were noted;

fibrosis of the anterior lip was more marked at the neck of the cervix. The uterus was hard with irregularities on the anterior surface and both sides. On the left posterior surface at the junction of the neck and lower uterine segment there was an indefinite mass. Adnexa: masses were felt at both cornua suggestive of bilateral salpingitis; the ovary on the left was not definitely made out but seemed distinct from the mass at the cornu and apparently was prolapsed and slightly enlarged; what seemed to be a definite cystic ovary was felt on the right side.

May 13th: Operation; (1) release of intestinal obstruction, (2) oophorectomy and salpingectomy, bilateral. Paramidline incision, pubis to umbilicus. The upper abdomen was apparently negative, the lower abdomen a mass of adhesions. The uterus and adnexa were hidden by adherent intestinal loops. The bladder wall was much inflamed. At the left cornu of the uterus the bladder, tube and an epiploic appendage of sigmoid were involved in a suppurating area which might have been a diverticulum of the bladder; however, separation showed the bladder wall apparently intact and the raw area was covered by peritoneum. Both tubes and ovaries were found oozing pus. It was not possible to save any portion of either ovary so both tubes and ovaries were removed. There were thick, indurated masses involving the sigmoid and ileum, all matted together with these suppurative tubes and ovaries. Many areas looked malignant but the condition was considered probably entirely inflammatory. Upon completion the pelvis was dry and the intestine patent throughout. Raw areas were reperitonealized and the sigmoid arranged behind the uterus to prevent entry of the small intestines into the pouch of Douglas. Closure in layers. The patient's condition was good on return to the ward.

June 3rd: X-ray showed the chest to be negative for pulmonary pathology.

June 9th: Discharged, the wound having healed by first intention.

Pathologist's Report

Gross Examination: The specimen, as received in 10 per cent formalin, consisted of one tube with an ovary attached and another tube and two separate (ovarian?) tumor masses. The tubes were thick-walled, congested and edematous. Both ovaries showed large, pale tumor masses considered probably carcinoma, at first. Later examination showed these to consist of multiple yellowish lobules, partially encapsulated and partially confluent, with strands of dense white tissue between the lobules and numerous small ragged foci in the centers of the cut surfaces of these lobules. Some similar foci were seen in the walls of both tubes. In the ovary adherent to the tube a large corpus luteum was noted.

Microscopic Examination: Multiple abscesses are seen in the ovaries and tubes, with granulomatous walls. There is no evidence of malignancy. The ovaries are chiefly involved. Although no

actual granules can be seen in a limited number of sections of tube, however, there are multiple abscesses in the walls, pus in the lumens, granulomatous walls about the abscesses and the inflammatory picture is identical with that seen in the ovary. One large granule is seen at the edge of the ovary very close to the tubo-ovarian adhesion. The smaller fungus granules are composed of centers that are not remarkable when stained with hematoxylin-

TABLE II

Other Cases Published or Referred to in the Literature, Not Included in Table I

No.	Author	Date of publication	Reason for omission from table
1	Bostroem	1890	Apparently same case as Middeldorpf's No. 4
2	Regnier	1894	Genitals not stated involved
3	Lieblein	1900	Skin of external genitalia involved only
4	Bongartz	1902	Vulva involved only
5	Trapl	1913	Right labium involved only
6	Reifferscheid	1924	Cannot locate with reference given
7	Richter	1927	Does not specify involvement of female genitalia

eosin but show innumerable, intertwining Gram-positive hyphae when stained by MacCallum's method for demonstrating Gram-positive and Gram-negative organisms. At the periphery of these granules the threads extend between adherent pus cells and can be seen in irregular broken form, with coccoid and bacilliform portions. Some of the small separate fragments are diphtheroid in appearance. In some sections the peripheral clubbed eosinophilic encapsulation of these hyphae is well demonstrated but in the larger clubs no filaments can be seen. One additional notation is made, not found described elsewhere. This is the large crystalline structure of the centers of the older colonies, these staining with eosin, being somewhat radial in distribution and having branched, spike-like peripheries. Such structure is seen in sections of the same granules with both stains and occupies most of the granule, only the periphery presenting many filaments. These were considered deposits of unknown composition.

Diagnosis: Actinomycosis of ovaries and tubes.

Subsequent History *

The patient has been carefully followed and has remained in excellent health since discharge from the hospital in 1929. She was last reported on April 25, 1933, at which time she weighed 155 pounds, stated that she was not constipated and on careful pelvic examination no tenderness, masses, induration or fixation could be detected.

Summary

1. Seventy-one published cases of actinomycosis of the internal female genitalia are listed.

2. Of these 45 individuals died, 8 were improved, in 7 the outcome is doubtful, and only 11 are possible cures.

3. The case reported showed involvement of both tubes and ovaries. The patient was operated upon and treated by potassium iodide, and is well 4 years after operation.

4. Tabulation of some features of published cases is presented.

Note: It is desired to express appreciation of the courtesy and cooperation of the following officers: Lt. Colonel F. S. Wright, M.C., who was Chief of the Surgical Service at Letterman General Hospital and who performed the salpingo-oophorectomy, Major H. S. Villars, M.C., who was Ward Surgeon at that time, and Colonel R. F. Metcalfe, M.C., at present Chief of the Surgical Service at Letterman General Hospital and who has kindly examined the patient several times for the author.

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* Since this article was submitted for publication, subsequent examination of the patient on April 17, 1934, showed her to be in excellent health; her weight was 153 pounds and there was no evidence of pelvic or abdominal masses. Hence this case has remained well for 5 years after operation, with no evidence of recurrence.

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DESCRIPTION OF PLATES

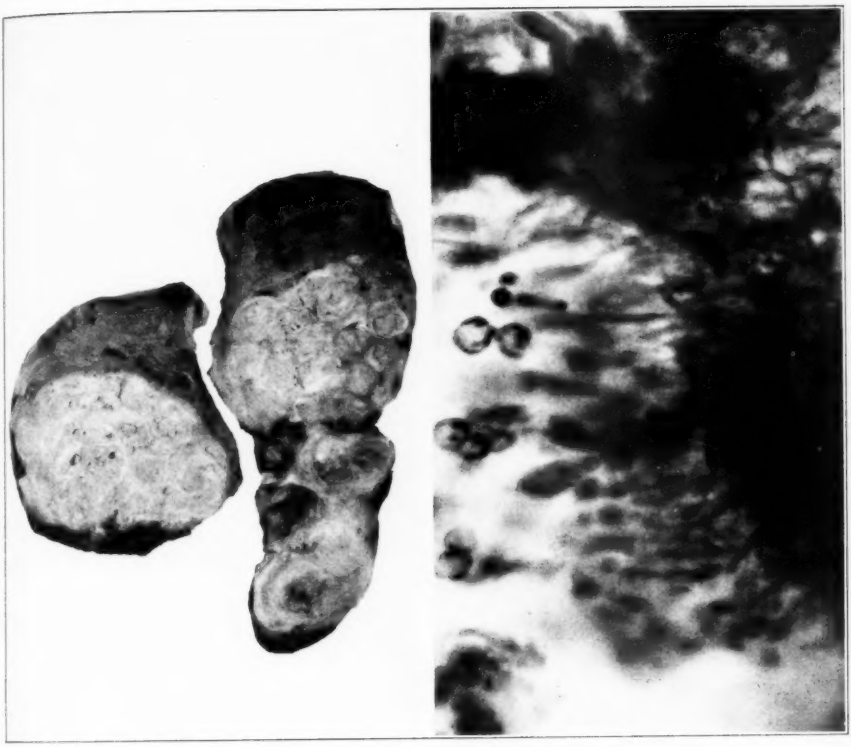
PLATE 128

FIG. 1. Ovarian and tubo-ovarian masses in gross. Note the fibrosis, alveolar arrangement and minute central foci of necrosis. Natural size. (Army Medical Museum Neg. No. 49885.)

FIG. 2. Higher magnification of upper edge of granule seen in Fig. 3, showing hyphae in more detail and extending into the clubs. MacCallum's stain. × 2000. (Army Medical Museum Neg. No. 49884.)

FIG. 3. Fungus granule showing mycelial maze of hyphae; hyphae extending into clubs and cellular reaction, chiefly polymorphonuclears. MacCallum's stain. × 810. (Army Medical Museum Neg. No. 49883.)

FIG. 4. Edge of granule showing higher power view of clubs. Hematoxylin and eosin stain. × 2000. (Army Medical Museum Neg. No. 31018.)



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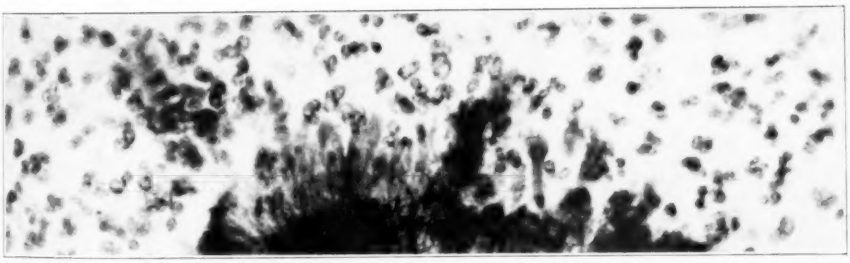

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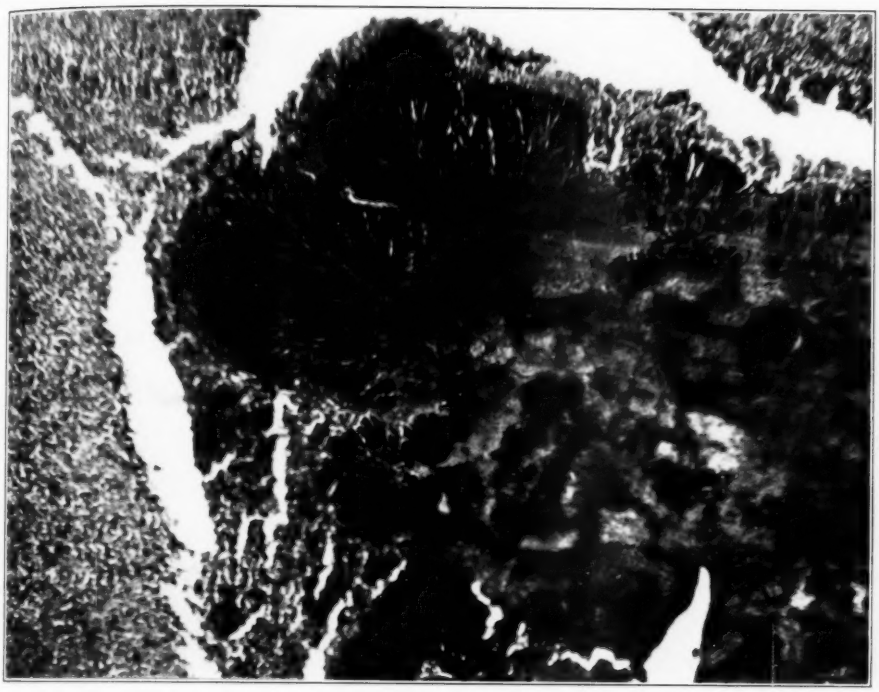
4

Cornell Actinomycosis of Tubes and Ovaries

PLATE 129

FIG. 5. This granule is mostly composed of the crystalline deposit, unidentified, not found previously described. About the periphery hyphae still exist. Note purulent wall about granule. Hematoxylin and eosin stain. × 91. (Army Medical Museum Neg. No. 48172.)

FIG. 6. Higher magnification of left edge of granule in Fig. 5, showing crystalline deposit in greater detail. The zone between this and the cellular exudate is a mycelial mass. Hematoxylin and eosin stain. × 515. (Army Medical Museum Neg. No. 48171.)



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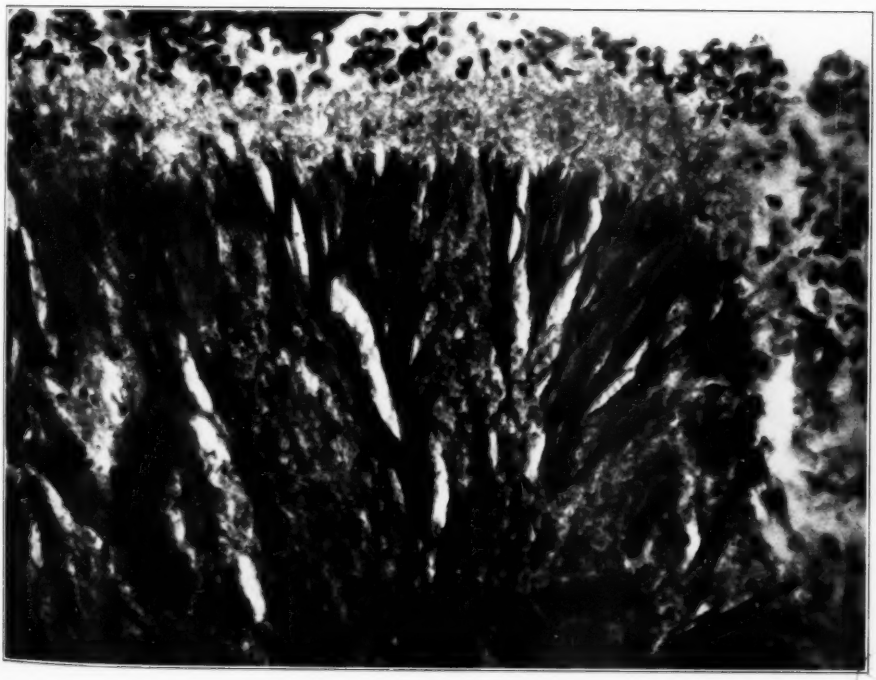

6

Cornell

Actinomycosis of Tubes and Ovaries

EXTRAGENITAL CHORIONEPITHELIOMA IN A MALE*

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The existence of a primary extragenital chorionepithelioma in the male has been questioned by Prym and by Oberndorfer in their recent writings. Both declare that extragenital chorionepithelioma in the male, when present, is always consequent upon a primary tumor in the testis. The case here reported, however, appears to fulfill all the requirements necessary to establish the primary extragenital origin of such a tumor.

REPORT OF CASE

Clinical History: No. 7813. B. L., a reporter, aged 22 years, was admitted to the medical service of the Mount Sinai Hospital with a harassing cough productive of thick mucoid sputum for 15 months. A postnasal drip was present at the onset. A tonsillectomy had been done with no symptomatic relief. For 13 months the cough became progressively worse and the sputum increased in amount. Two months ago the sputum became blood-streaked and pain appeared in the lower anterior chest. Two weeks prior to his admission to the hospital he awoke feeling chilly. He coughed up blood which, he was certain, came from his lungs. An obstinate anorexia, nausea and vomiting occurred with attempts to eat. A progressive dyspnea and orthopnea appeared. He lost 25 pounds in weight in the 2 weeks. His temperature rose slightly 1 day before admission.

Physical examination revealed a young man, well nourished, cyanotic and dyspneic (respirations 40). Attacks of hacking cough and vomiting were precipitated by movements in bed. There was a slight right exophthalmos. There was no tracheal deviation or fixation. The veins of the neck were engorged. The thyroid was normally palpable. The chest showed moderate emphysema. There was slight dullness and diminished fremitus throughout. There were occasional inspiratory crepitant râles present at the angle of the right scapula and anteriorly below the nipple. The heart was negative. Irregularly distributed tenderness was present throughout the entire abdomen. The right testis was small and firm; the left was slightly larger. The prostate was enlarged, but not tender or firm. There were irregularly distributed sites of tenderness over the sternum, right lower costal margin extending upward to the nipple, and both humeri.

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Clinical Diagnosis: Metastases to lungs and bones from a primary malignant tumor in the prostate or nasopharynx.

Laboratory Data: Blood pressure 112/70. Blood count: hemoglobin 72 per cent, white blood corpuscles 23,000, polymorphonuclear leukocytes 91 per cent. Sputum negative for tubercle bacilli. Urine negative. Blood Wassermann negative. Urea nitrogen 15 mg. per 100 cc., calcium 8.1 mg. per 100 cc., phosphorus 4 mg. per 100 cc. Roentgenograms of the skull and femur showed no evidence of metastases; the chest showed the lungs to be closely studded with metastatic newgrowths which varied in size from 0.5 to several cm.

The patient became progressively worse and died 5 days after admission.

Autopsy Report

Autopsy performed 12 hours postmortem. The body is that of a white male, 22 years of age, in complete rigor mortis, rather heavily built and well nourished. He has a moustache and a normal male distribution of facial, pectoral and pubic hair. The genitals are those of the normal adult male. The breasts are not enlarged. Bloody froth exudes from the mouth. No clubbing of the fingers is seen. The head and neck seem moderately swollen.

Abdomen: The panniculus adiposus is of normal thickness. The peritoneum is smooth and glistening and contains no excess of fluid. The situs viscerum is normal. The diaphragm reaches to the fifth rib on the right side and to the fifth interspace on the left.

Chest: No fluid or adhesions are found in the pleural spaces. Both lungs are crowded with large, firm, circumscribed nodules, varying in size from 0.5 to 3 cm. in diameter, with the majority about 2 cm. (Fig. 1). Those near the surface bulge outward, the intervening lung being depressed. Some show slight umbilications. Even throughout the pleura hemorrhagic spots are seen in some of the nodules. On section the nodules extending throughout the depth of both lungs are seen to be sharply circumscribed in the deeply congested and fleshy lung tissue. The cut nodules show an irregular mottling of grayish pink tissue with intervening vacuolated areas containing fluid blood. The larger branches of the pulmonary artery are normal. The trachea and bronchi contain bloody froth.

In the superior mediastinum (Fig. 1), just superior to the heart, an irregularly rounded mass of firm tissue 8 by 5 by 4 cm. is seen. The long axis is parallel to the trachea. Although adherent to the adjacent structures (pleural pericardium and vessels), it may be partly separated until it is revealed as lying between the superior

vena cava on the right, trachea and aorta posteriorly and the pericardium inferiorly. The two flaps of thymic fat adhere to the superior surface of the mass. There does not appear to be invasion of the adjoining structures by the tumor. Sections of the mass reveal an irregularly trabeculated surface similar to the cut surface of the pulmonary nodules. Small lakes of fluid hemorrhage are seen throughout the supporting trabeculations, which are grayish pink. Scattered throughout the mass are small circumscribed nodules of varying size. In the lower pole one of these nodules reaches the size of a pea and is distinctly circumscribed. It is grayish yellow in color and much firmer in consistence than the remainder of the tumor mass. Areas of necrosis and fibrosis are seen. At the inferior pole the hemorrhagic and necrotic tissue is replaced by firm white tissue with cyst-like spaces varying in diameter from 0.5 to 2 mm. This almost occludes the superior vena cava and grows upward into the left innominate vein.

Heart: The pericardium contains no excess of fluid. The superior portion of the parietal pericardium is reddish and slightly roughened where its external surface is adherent to the tumor mass. The subepicardial fat is normal in amount and distribution. The right ventricle is moderately dilated and hypertrophied. The columnae carneae and papillary muscles are prominent. The endocardium and valves are normal. The myocardium is firm and grayish red. The coronary arteries and their orifices are patent. The aorta is elastic and contains no plaques. The pulmonary arteries show a few intimal thickenings.

Liver: Weight 2020 gm. It is smooth and of normal consistence. The central lobular areas show a deep brownish red color. No metastases are found.

Pancreas: Normal.

Spleen: Weight 275 gm. The cut surface shows a deep red pulp in which the follicles are large and prominent.

Genito-Urinary Tract: Both kidneys together weigh 325 gm. They present a normal appearance. The pelves, ureters, bladder and prostate are normal. The testes are slightly smaller than normal. The epididymis and testes contain no nodular enlargements or areas of hemorrhage. The rete and vas deferens are grossly negative, presenting no tumors or areas of hemorrhage. The seminal vesicles show no abnormality.

Adrenals: Normal.
Gastro-Intestinal Tract: Normal.
Bone Marrow: Normal.

Biological Examination

Twelve hours postmortem:

Urine: A positive Aschheim-Zondek test was obtained in four mice with quantities of urine varying from 1.5 to 2.4 cc.

Tumor Tissue (Lung Metastases): Ether extract for the female sex hormone (Frank) was negative with 20 gm. of tissue.

Alcohol extract for the anterior pituitary hormone with 1 cc. equivalent to 9.5 gm. of tumor tissue: two mice gave positive results with 1.2 cc., one was negative with 0.5 cc.

Microscopic Examination

Tumor Mass: In its inferior portion many types of epithelial structures are seen. They vary from solid nests of undifferentiated epithelial cells to cyst-like spaces lined by squamous epithelium. There are gland-like structures with low cuboidal, high columnar, and pseudostratified epithelium. Occasionally the high columnar epithelium is ciliated (Fig. 2).

The remainder of the tumor mass is almost entirely necrotic. At the periphery of the necrotic areas cell masses with deeply staining acidophilic cytoplasm appear in syncytial arrangement. The nuclei are irregular in form and are hyperchromatic. The cytoplasm appears in masses, elongated strands and ramifying networks. Isolated cells and multinucleated giant cells are also seen, especially in the necrotic areas. Plaques of cells with definite boundaries and vacuolated dust-like cytoplasm are present. Their nuclei are vesicular, and have a definite nuclear membrane with one or more coarse chromatin clumps (Fig. 3). The proportions of the two types vary; frequently the plaques of cells are completely surrounded by the syncytially arranged acidophilic cytoplasm. The plaques of cells are identical with the Langhans cells seen in the uterine and in the testicular chorionepithelioma. The syncytial cytoplasm appears to be more hardy since it occurs alone in the midst of necrotic areas. That these are not advancing cytoplasmic columns may be surmised from

the presence of degenerating and degenerated cell plaques. Occasionally cilia-like projections are seen on the syncytial cytoplasm. Both types of cells are seen in the small veins, occasionally even where the wall has been destroyed and a small thrombus occludes the vessels. Calcific foci are seen in the necrotic areas. Glycogen stains give negative results (tissue fixed 12 hours after death).

Thymus: Shows normal structures with increased amount of fat in the trabeculae. Occasional veins in the fat and connective tissue show syncytial cytoplasm similar to that seen in the masses.

Lungs: The nodules in the lungs show complete central necrosis surrounded by alternating areas of necrosis and hemorrhage. Around this zone is another with hemorrhage, necrosis and bands of acidophilic cytoplasm with hyperchromatic nuclei in single cell and syncytial arrangement. External to this there are plaques of cells with definite cell boundaries, vacuolated or dust-like cytoplasm and round or oval vesicular nuclei with sharp nuclear membranes and one or more coarse chromatin clumps. Mitoses are seen. Covering these plaques, identical with the Langhans cells of the primary mass, are the syncytial masses of acidophilic cytoplasm with hyperchromatic, irregularly shaped nuclei. Mitotic figures are frequent. Occasionally, under oil immersion magnification, cilia-like projections are seen on the syncytial cytoplasm. The picture is identical with the typical chorionepithelioma of Marchand. The boundaries of zones are not rigid but merge indefinitely with each other. In none of many lung sections are teratomatous elements present.

Zones of compressed lung tissue surround the nodules. The pulmonary arteries contain syncytial masses of cytoplasm. Alveoli filled with fibrin, polymorphonuclear leukocytes and pigment-laden phagocytes are seen, with occasional polymorphonuclear leukocytes and fibrin-filled bronchi.

Lymph Nodes: Neither the thoracic nor the retroperitoneal nodes show tumor metastases. There is sinus endothelial hyperplasia with marked erythrophagocytosis.

Testes: Both testes were cut in 2 mm. blocks and embedded. The entire testes were thus cut. Slides were cut from each block. No tumor nodules or scars were found. A marked hyperplasia and hypertrophy of the Leydig cells is present throughout both testes (Fig. 4). There are nodules of interstitial cells which reach 500 microns in diameter. The tubules show spermatogenesis. Numerous

atrophic tubules are present. Within their lumens are bodies with concentric rings of calcification. The rete and epididymis show no changes.

Prostate and Seminal Vesicles: Sections through the prostate show adenomatous hyperplasia with papillary proliferations in the lumen. There are no tumor nodules.

Liver: The central lobular areas show congestion with atrophy of the liver cell cords.

Spleen: The follicles are normal. There is slightly increased cellularity of the pulp with increase in the polymorphonuclear cells. The sinuses and pulp spaces contain much blood. The sinus walls are prominent, the intersinusoidal spaces are widened and the cytoplasmic reticulum is conspicuous.

Kidneys: Marked congestion of the cortex and medulla is present.

Pancreas, Adrenals, Thyroid: No changes are seen.

Breast: Tissue taken from immediately beneath the right nipple shows only fat and connective tissues with nerves and blood vessels. No glandular structures are seen.

Discussion

Cases of extragenital chorionepithelioma in males have been published by Bostroem in 1902, Ritchie in 1903, Askanazy in 1906, Bonney in 1907, Fischer in 1908, Nakayama in 1910, Weber in 1918, Lambert and Knox in 1920, Miller and Browne in 1922, Krassnianskaya in 1929, Schultze in 1930, Arendt in 1931, and Heaney in 1933. A critical examination of their protocols suggests the possibility that a primary origin from the testicle may have been overlooked in a number of instances.

Bostroem himself now doubts the interpretation originally published for his case of intracranial chorionepithelioma, since he believes an incomplete examination of the testicles was made.

Askanazy's case of pineal teratoma had no testicular examination.

Frank's Case III, with a mediastinal mass, had no testicular examination. There was also an incomplete examination of the mediastinal tumor, since only necrotic tissue was found.

The omental tumor and its metastases in the case described by Bonney showed only chorionepitheliomatous tissue. The testicles were incised and found negative grossly. This observation was not controlled by histological examination.

Fischer found a retroperitoneal tumor in a male with an absent right testis. He was probably dealing with an abdominal testicle with chorionepitheliomatous neoplasia.

Nakayama observed a patient with a retroperitoneal chorionepithelioma demonstrated at the operating table. There was no examination of the testes.

Weber's patient had a retroperitoneal tumor with liver and lung metastases. Portions of organs were sent to the author for examination. The lumbar lymph glands made up the mass. No teratomatous elements were noted. One should hesitate to accept the conclusions drawn by the author since he was the recipient of incomplete postmortem material.

Schultze considered a nodule in the right testicle to be a metastasis from a primary retroperitoneal tumor, an obviously incorrect interpretation.

The statistics of Greiling compiled from a study of 220 cases of malignant tumors of the testicle with metastases show retroperitoneal involvement in 100 per cent of the cases. Such figures justify one in doubting the validity of the reported cases of primary retroperitoneal chorionepithelioma with no or incomplete testicular examinations. The fact that brain metastases occur in 5.9 per cent of the cases also throws doubts on the reports of cerebral chorionepitheliomas without testicular examinations. These considerations lead me to a critical review of the remaining 6 cases.

In the cases of Ritchie and of Lambert and Knox there were present tumors containing teratoid and chorionepitheliomatous elements. In both cases the tumors were situated in the anterior mediastinum (a location not mentioned by Greiling in any of the 220 cases with metastases). This similarity to the tumor here reported would suggest the possibility that there were cases of primary extragenital chorionepithelioma in males, were it not for the absence of testicular examinations. In this connection the experiences of Prym and Ewing make one hesitant in accepting cases of this type. The former, in 1927, described a case of chorionepitheliomatous metastases from a small tumor of the right testis which had healed spontaneously. Microscopic examination of the testicular nodule revealed only elastic and connective tissue fibers. The common experience with spontaneous regression of female chorionepitheliomas should lead one to accept Prym's interpretation. Ewing has seen "a medi-

astinal teratoma secondary to a small testicular growth which escaped several examinations during life." He writes further: "Some reported abdominal and thoracic teratomas may possibly represent metastatic growths from minute teratomas of the ovary or testis."

Miller and Browne in 1922 reported a retroperitoneal chorionepithelioma in a male. Microscopically the tumor was a typical chorionepithelioma. Both testicles were found to be normal after careful examination. There were metastases in the retroperitoneal lymph nodes and liver.

Krassnianskaya in 1929 reported a primary tumor at the hilum of the left lung. There were generalized metastases in the spleen, kidneys, retroperitoneal lymph nodes, adrenal glands and brain. The prostate was small but normal. Both testicles were in the scrotum. Very thin sections of both testicles and epididymi showed no changes, grossly or microscopically. The tumor and its metastases showed the characteristic picture of the chorionepithelioma. The primary tumor and its metastases showed no evidence of a teratoma. On this basis Krassnianskaya believes that he has observed a pure chorionepithelioma in an extragenital location in a male. He attempts to divide the extragenital chorionepithelioma into two types: those that are pure and those that contain teratomatous elements. This classification I believe to be fallacious in view of the difficulty in determining the previous presence or absence of teratomatous elements. The experiences with chorionepithelioma of the testicle demonstrate how readily the components of a teratoma may be destroyed by the invading chorionepitheliomatous elements.

Arendt, in 1931, described a mediastinal teratoma with chorionepitheliomatous metastases in the lungs and liver. His patient was 20 years of age and had complained of bloody sputum 2 months before admission. Gynecomastia was present. On physical examination the testicles were hard and about 2 by $1\frac{1}{4}$ cm. in diameter. At autopsy a tumor about 3 cm. in diameter was found in the anterior mediastinum. It extended into the left lung and pericardial sac. Grossly the tumor resembled a chorionepithelioma. Both testicles were grossly atrophic. Microscopically the testes showed an atrophy of the tubular elements with a marked proliferation of Leydig cells. There were no biological tests performed. The presence of a mediastinal tumor with chorionepitheliomatous metastases in the lungs

and liver with negative testes (grossly and microscopically) appears to answer the strictest criteria for the presence of primary extragenital chorionepithelioma in a male.

Heaney in 1933 observed a male, aged 40 years, with a large retroperitoneal tumor. The patient died subsequent to an operation for the removal of the mass. The anatomical diagnosis was that of primary retroperitoneal chorionepithelioma probably derived from the urogenital anlage. The inferior vena cava and left renal vein were filled with tumor tissue. There were metastases in the lungs. The right testicle was atrophic. Microscopically the tumor closely resembled a typical chorionepithelioma. There were no teratomatous elements present. The left testicle showed a hyperplasia of the interstitial cells. An area of new hemorrhage, blood pigment and fibrin was found. This is interpreted by the author as probably the result of an old trauma. No evidence of tumor tissue was found. There was no retroperitoneal lymph node involvement. The author was fully aware of Prym's stand and states that "testicular involvement has been excluded with certainty in this case."

In summary it appears that the cases of Miller and Browne, Krassnianskaya, Arendt and Heaney appear to fulfill the criteria necessary for the diagnosis of a primary extragenital chorionepithelioma in a male.

The case here reported belongs in a similar category. The presence of a teratomatous tumor in the mediastinum with metastases to the lungs and the absence of tumor, active or healed, after careful macroscopic or microscopic examination of the genital tract, including the prostate, seminal vesicles, vas deferens and testes, should be sufficient to justify this conclusion, especially when one considers that both testes have been cut and blocked in their entirety in 2 mm. sections. Furthermore, the absence of metastatic chorionepithelioma below the diaphragm, grossly and microscopically, also the absence of thoracic and retroperitoneal lymph node involvement speak against the presence of a focus other than the anterior mediastinum. Additional support to this view is furnished by the observations of Smith, who has collected 147 cases of mediastinal dermoid cysts and teratomata with 12 showing malignant neoplastic growth. Thus one can see no reason, on theoretical grounds, why a mediastinal teratoma cannot have chorionepitheliomatous elements. The microscopic examination of the primary tumor and the pul-

monary metastases shows a structure identical with the typical chorionepithelioma of Marchand. The acidophilic syncytium, the plaques of Langhans cells, the hemorrhagic character, and the areas of necrosis all indicate that it is identical with the Marchand chorionepithelioma. The microscopic picture coincides, too, with the descriptions of testicular chorionepithelioma by Wlassow, Risel and Schlagenhaufer.

Biologically the case presented is similar to the uterine and testicular chorionepitheliomas. The tissue extracts and urine gave positive Aschheim-Zondek tests. The female sex hormone test of Frank was negative. Increasing numbers of positive Aschheim-Zondek tests in testicular chorionepithelioma have been reported. Heidrich, Zondek, Kriss, Hady, Ehrhardt and Frank report positive results. Ferguson reports positive Reaction I (prolan A) tests with testicular teratoma and the embryonal carcinomas of the testis (seminoma of Chevassu). Thus far one may agree with Heidrich, Fels and Mathias that certain neoplasms of the testis cause the excretion of a hormone whose presence in the urine and, one may add, in tumor tissue extracts, can be detected readily by biological means. The positive results reported with certain genital and extragenital malignant growths are not the Reactions II and III of Zondek, but merely Reaction I. The latter result may be obtained with rapidly proliferating tumors, in diminished genital function at the beginning of the menopause and in certain types of amenorrhea. It consists of cystic enlargement of the ovaries in immature rodents usually combined with oestrus production and follicle growth. It is not indicative of pregnancy. Reactions II and III show hemorrhagic follicles (blood points) and corpus luteum formation, respectively. Teratoma testis with chorionepithelioma and the embryonal carcinoma of the testis give Reactions II and III. Reaction I (prolan A) is found in conjunction with too many conditions to be of aid in the diagnosis of testicular tumors, although its importance in the determination of the extent of the disease and the effect of treatment for teratoma testis is amply demonstrated by Ferguson.

An interesting observation is that of the marked hypertrophy and hyperplasia of the interstitial cells of the testes. This was marked throughout the testes, resulting in diffuse strands and nodules up to 500 microns in diameter. Arendt and Heaney also report a marked proliferation of Leydig cells with almost tumor-like growths. Wlas-

sow, Risel, Dillman and Hedinger have also observed the marked proliferation of the Leydig cells in testicular chorionepithelioma. The occurrence has been noted in other conditions but its significance remains unknown.

Gynecomastia has been reported with teratogenous chorionepithelioma. It was not present in this case.

Summary and Conclusions

A case report with autopsy findings in a male aged 22 years with a primary teratoma of the anterior mediastinum containing chorionepitheliomatous elements is presented. The tumor invaded the superior vena cava, studding both lungs with chorionepitheliomatous nodules.

Careful gross examination revealed no metastases in the other organs or lymph nodes. The genital tract (testes, vas deferens, seminal vesicles and prostate) showed no tumor nodules. The testicles were sectioned in 2 mm. blocks and slides were made from each block. Examination revealed no tumor nodules.

Microscopic examination of the tumor revealed teratomatous and chorionepitheliomatous elements. Only chorionepithelioma was found in the pulmonary metastases. The testes showed no neoplastic elements. Marked interstitial cell hyperplasia of the testes was seen.

These observations refute the contention of Prym and Oberndorfer, the latter writing "dass beim Mann das Chorionepitheliom immer mit Keimdrusengeschwülsten in Zusammenhang stehen muss."

The Aschheim-Zondek test was positive in both the urine and tumor tissue extracts.

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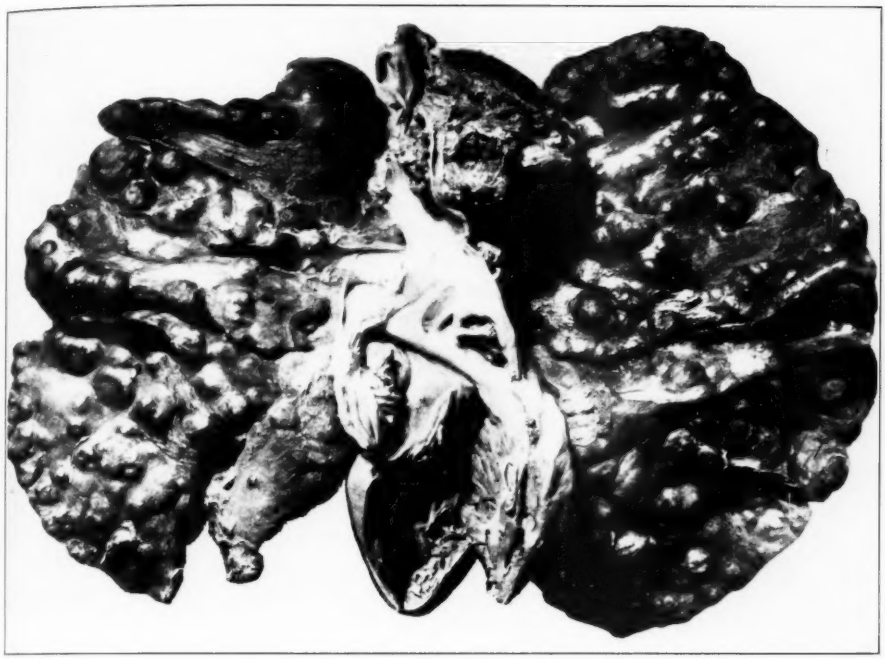
DESCRIPTION OF PLATES

PLATE 130

FIG. 1. Tumor mass in the superior mediastinum with erosion into the left innominate vein. Lungs with metastatic nodules.

FIG. 2. Teratomatous structures in the inferior pole of the mass.



1

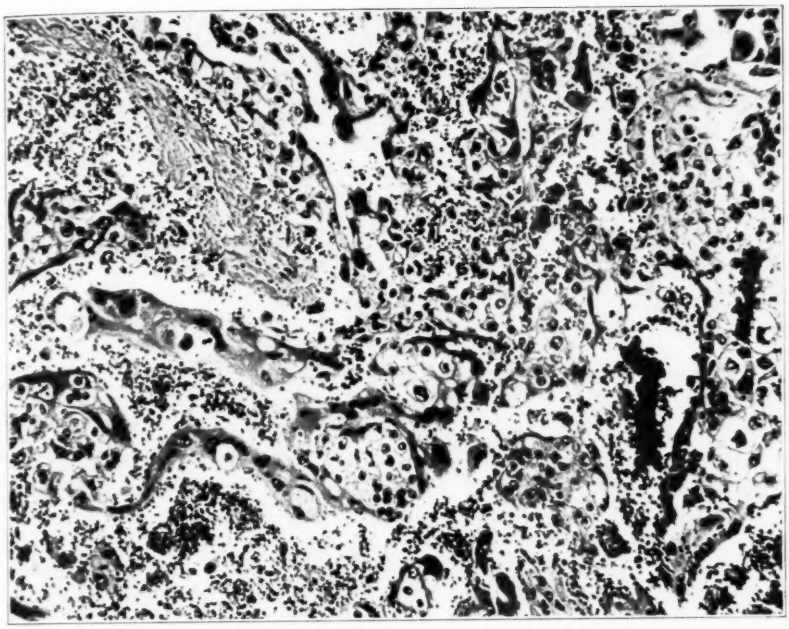
2

Kantrowitz Extragenital Chorionepithelioma in a Male

PLATE 131

FIG. 3. Plaques of Langhans cells with syncytial cytoplasm, from the upper pole of the mass, representing elements of typical chorionepithelioma.

FIG. 4. Hyperplasia and hypertrophy of the interstitial cells of the testis.



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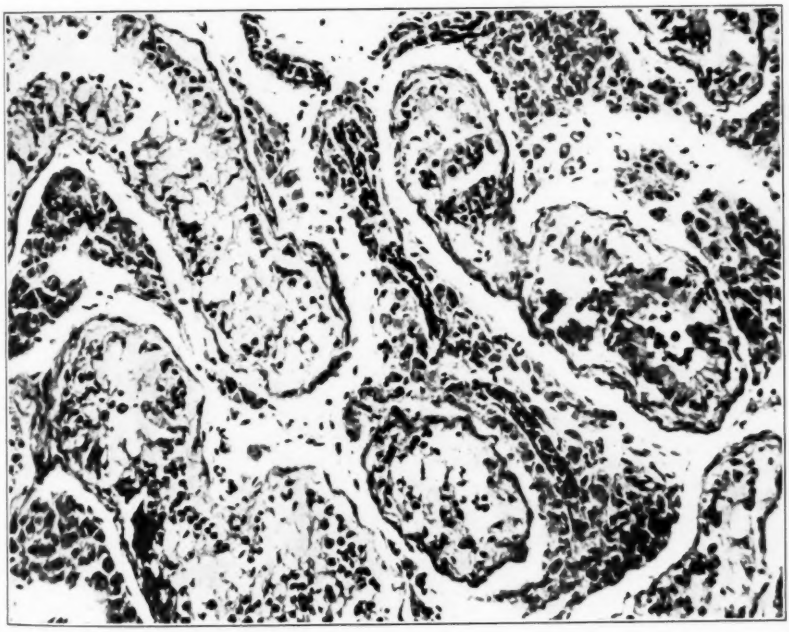

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Kantrowitz Extragenital Chorionepithelioma in a Male

MULTIPLE HEMANGIOBLASTOMAS OF THE SPINAL CORD WITH SYRINGOMYELIA *

A CASE OF LINDAU'S DISEASE

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In 1926 Lindau described a syndrome whose chief feature was an angiomatosis of the central nervous system. Brandt and Berblinger had previously noted this disease entity but had failed to describe it thoroughly or to emphasize its distinctness. In this condition cystic or solid hemangioblastomas of the cerebellum, brain stem or spinal cord, single or multiple, were found associated with angiomatosis of the retinae (von Hippel's disease) and concomitant malformations or tumors in the somatic organs. The latter were described as cystic pancreas, cystic kidneys, cysts of the liver, hypernephromas and adenomas of the kidneys and adrenals, and cavernomas of the liver. Lindau described 15 cases in all. Ten were collected from the literature and had been variously described and classified. Five were cases of his own. He showed that there was a distinct familial incidence of the disease and that the average age of onset of symptoms was about 30 years. In 4 of the 15 cases hemangioblastomas of the cord were present (Wersilow, Brandt, Tannenberg and Koch). In all 4 the cord tumors were multiple and in 3 were associated with lesions outside the nervous system, of the type described above (Brandt, Tannenberg and Koch). In only 1 case was there an associated syringomyelia of the cord (Tannenberg). Since Lindau's report 4 more cases of hemangioblastoma of the spinal cord have been described (Guillain *et al.*, Schuback, Kernohan *et al.*, and Russell). Two presented lesions characteristic of Lindau's syndrome (Schuback, and Kernohan *et al.*). There are thus only 3 cases of Lindau's disease in the literature to date in which hemangioblastomas of the cord were associated with syringomyelia. The following is the report of a 4th case.

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Report of Case

Clinical History: E. W., (P. H. No. 312177), male, 33 years of age, was admitted to the Presbyterian Hospital complaining of numbness in the arms and legs and griping pains in the abdomen.

His father had died of brain tumor at the age of 36 and his mother of "spinal meningitis" at 28 years of age. A twin brother and sister had died at birth.

Twelve years prior to his present illness the patient struck his head while diving and was unconscious for a short time. Detachment of the right retina occurred and he underwent twelve operations until the right eye was finally enucleated 6 years prior to the present illness. Two years later detachment of the left retina occurred and that eye was enucleated. This was unassociated with further trauma.

During the year before admission the patient developed slight unsteadiness on his feet with a tendency to fall to the right, and tremor of the hands on performing skilled acts. Constipation, which had been present for years, grew increasingly severe. There were recurrent attacks of vertigo. Numbness of the right arm and leg and of the left foot developed 5 months before admission. Severe griping and stabbing pains occurred, starting at the umbilicus and radiating to the flanks, accompanied by a compressive girdle sensation. He grew progressively weaker, losing 13 pounds in the last few weeks before his entry to the hospital.

On admission he was quite weak, and gait and station could not be tested. All the coordination tests were inconclusive for the same reason. There was great weakness of all the muscles of the four extremities, more marked on the right side. Hyperreflexia was found in the left upper and both lower extremities with increased muscular tone. The upper abdominal reflexes were diminished and the lower abolished. The Babinski test was positive on the right and questionable on the left. The interossei muscles of the right hand, all the muscles of the right forearm, the right biceps, triceps, supra- and infraspinati and posterior portion of the deltoid muscles showed a well marked atrophy. On the left there was moderate atrophy of the interossei and slight atrophy of the forearm muscles and supra- and infraspinati. Direct muscular irritability was definitely increased in the atrophic muscles.

Vibratory sensibility was slightly impaired below the patellae in both lower extremities. The sense of position was slightly diminished in the toes. Perception of pain and temperature was completely lost from the eighth thoracic segment up to the fourth cervical on each side. It was considerably diminished up to the first cervical segment on the right and third cervical on the left, and moderately diminished down to about the first lumbar segment. Touch was only slightly impaired, if at all. There was difficulty in swallowing, which had developed recently, and questionable fibrillations of the tongue.

The spinal fluid pressure was 150 mm. Compression of the jugulars caused a rise to 190 mm. with a slow fall. Coughing brought the pressure to 240 mm. and straining to 300 with a very gradual drop. The fluid was xanthochromic, showed a 2 plus globulin, contained 5 cells and gave a 4 plus Wassermann test. The colloidal gold test resulted as follows: 1111122210. The blood Wassermann was negative.

The picture that the patient presented was thus typical of intramedullary disease of the spinal cord. The course seemed rapid for syringomyelia. The

diagnosis of medullary tumor was considered, but the positive spinal fluid Wassermann made it seem more probable that a gumma was present or that there was luetic thrombosis of the spinal arteries.

The patient developed an intractable hiccoughing a few days before death, and finally succumbed to a terminal bronchopneumonia.

Gross Autopsy Findings

Brain: The dura was somewhat tense, smooth and glistening throughout, and the dural sinuses were patent. The cerebral hemispheres were symmetrical. There was mild generalized flattening of the gyri and narrowing of the sulci. The pia was thin and translucent throughout. On section a mild dilatation of the lateral ventricles was noted. No lesions of the parenchyma were found.

The cerebellum appeared negative externally. On section a small, oval, smooth-walled cyst containing gelatinous yellowish fluid and measuring 17 by 10 by 5 mm. was found in the posterior portion of the central white matter of the lower half of the left cerebellar hemisphere. In the floor of the cyst a small mural nodule was found. It was soft, yellowish brown, had a rather smooth surface and measured 5 by 3 by 2 mm.

The greater portion of the brain stem appeared normal externally. The lower portion of the medulla from about the middle of the inferior olives downward was considerably increased in size, its diameters being almost twice the normal. The increase was greatest where the stem joined the cervical cord. The pia over the base of the stem was slightly clouded. A mild dilatation of the aqueduct of Sylvius and anterior portion of the fourth ventricle was noted on section. In the lower half of the dorsal portion of the medulla a ragged oval cavity was found containing clear yellowish fluid and measuring 4 by 11 mm. in cross-section at the junction of medulla and cord. It ended in the first cervical segment and its total length was 14 mm. About it was a narrow band of grayish translucent tissue varying in width from 0.5 to 1 mm. Most of the structures in this portion of the medulla were not identifiable grossly and the tissue had a grayish white, scarred appearance.

Spinal Cord: The pia was clear but the pial vessels were quite hyperemic. The cervical cord was considerably enlarged and this was most marked in the first four segments. Here it measured approximately 24 mm. transversely and 13 mm. anteroposteriorly. On

the dorsal surface of the second and third cervical segments to the left of the midline a flat, yellowish, soft tumor mass measuring 6 by 5 by 3 mm. was found (Fig. 1). Its margins were fairly sharp and it extended down into the posterior columns on the left side to within a short distance of the central canal. The white and gray matter at its margins was edematous, somewhat yellowish and softened. The outlines of the gray matter were indistinct at this level. Both gray and white matter had either a yellow or grayish white tinge and seemed edematous. Small zones of softening without cavitation were found in the posterior horns and occasionally in the anterior at the level of the tumor and above it up to the medullary cavity, which was described above as ending in the first cervical segment. In the fourth and fifth cervical segments single and multiloculated cavities were found involving the dorsal columns and posterior horns and lying dorsal to the central canal (Fig. 4). These were of the same character as the larger cavity in the medulla. They grew less extensive and numerous in the succeeding lower segments and ended in the second thoracic segment. The demarcation between white and gray matter became increasingly distinct and the cord grew less edematous. The rest of the thoracic cord looked somewhat irregular in caliber, but was of normal consistence. There was slight brownish discoloration of the posterior columns in the lower thoracic segments with petechial hemorrhages and small softened zones in the gray matter, particularly the posterior horns. In the tenth thoracic segment a small, grayish, granular tumor nodule 2 mm. in diameter was found in the right posterior horn (Fig. 2). At this level again there was edema and lack of clarity of the margins of the gray matter. In the next segment below this multiple central cavitations reappeared and gave place to a single large cavity in the first lumbar segment. This latter involved portions of the gray horns on the right, as well as parts of the white columns. It ended in the fourth lumbar segment and was 6 by 4 mm. at its widest point (Fig. 3). The walls of these lumbar cavities were wider, firmer, paler and more fibrous than that of the medullary cavity and varied in width from 1.5 to 2 mm. Their contents were the same as that of the bulbar cavity. Throughout this zone and for a short distance below it the gray and white matter had no very clear outlines. On the dorsal surface of the cauda equina and attached loosely to the fourth and fifth lumbar roots on the left was a small, yellowish, en-

capsulated tumor nodule measuring 4 mm. in diameter and resembling grossly the tumor in the cervical region.

Left Adrenal: The left adrenal was enlarged and almost spherical in shape, weighing 60 gm. On section a large, roughly spherical, moderately firm tumor, measuring 4.5 by 4 by 4 cm. was found within the gland. It was variegated in color, ranging from pinkish gray to yellowish brown, and was studded with many thin-walled blood vessels. It appeared to have arisen in the medulla and to have displaced the cortical tissue at its margins, so that only a thin rim of cortex intervened between the periphery of the tumor and the slightly thickened adrenal capsule. At either pole the normal adrenal tissue was better preserved. At the lower pole two smaller oval-shaped masses measuring 1 and 1.5 cm. in diameter, respectively, similar in all respects to the larger mass, were found. The right adrenal showed no abnormalities. A paraortic lymph node in the region of the left adrenal contained two small, irregular yellowish zones in its substance.

Kidneys: The kidneys were normal in size and appearance save for the presence of several tumor nodules. The largest of these measured 2 by 1.5 by 1 cm. and was situated on the posterior aspect of the right kidney near the hilum. Externally it appeared as a firm, grayish white mass embedded in the cortical surface. The cortical tissue at the margins of the mass was somewhat depressed and scarred. On section the mass was seen to be composed of an outer white fibrous shell measuring 2 mm. in diameter, and a central core made up of reddish and yellowish softer tissue in which a few small cystic spaces 1 to 2 mm. in diameter were present. The nodule extended into the medulla to a slight extent.

Beneath a small pit-like depression on the lateral aspect of the left kidney a small, firm, grayish white nodule measuring 3 mm. in diameter was seen. This contained two small, reddish foci. It resembled the larger nodule in the right kidney somewhat. A third nodule 1 cm. in diameter bulged above the cortical surface near the upper pole. It was composed of soft, grayish brown tissue, was encapsulated and contained several tiny cysts.

Pancreas: The pancreas was normal in size and shape. Several small, thin-walled cysts filled with clear fluid and situated close together were found in the body of the organ. The largest measured 3 mm. in diameter. The pancreatic duct was of normal caliber.

There was an anatomically patent foramen ovale. The liver contained no cysts nor did it show any other abnormalities.

In addition to the above findings there were bilateral lobular pneumonia, acute fibrinous pleurisy, and an acute splenic tumor.

Microscopic Examination

Tumor in Upper Cervical Cord: On the dorsal side of the cord, to the left of the midline, a highly vascular, moderately cellular tumor mass is found displacing a good portion of the posterior columns and distorting the cord considerably. It is fairly well demarcated. The predominant elements in its structure are blood vessels, capillary in type and fairly irregular in size and shape. Occasionally these lie approximated, but most frequently they are separated by one or more layers of intervening cells (Fig. 5). Some larger vascular channels are also present but their walls are composed of collagenous connective tissue with no evidence of arterial or venous structure. From these the surrounding capillaries are often found to radiate (Fig. 9). The capillaries, as noted above, are quite irregular with much branching and outpocketing. They are lined by a single layer of endothelium. This varies from flat, elongated cells with oval, dark, concentrated nuclei, to full-bodied epithelioid-like cells with oval, vesicular nuclei. These frequently seem to merge intimately with the intervascular elements. There is no endothelial hyperplasia, however, nor are any mitotic figures noted in the cells of the capillary walls. Their lumens are either empty or contain varying numbers of erythrocytes. In none of the vessels are any immature blood cells noted. The walls of the larger channels described above are at times quite thick and occasionally hyalinized. The cellular elements found between the vessels are chiefly large-bodied, polygonal and spherical with vacuolated, foamy cytoplasm (Fig. 7). The nuclei are comparatively small, concentrated, often compressed at the periphery of the cell and so lunate-shaped. In other cells again the nuclei are more centrally placed and angulated, presenting concave surfaces due to compression by the lipoid globules. Where these lipoid-laden cells are particularly abundant and most heavily vacuolated, the capillaries between them are compressed, though numerous, and at first glance seem to form only an insignificant portion of the picture (Fig. 8). The lipoid material in these cells is found to be a mixture of neutral fats and finer lipoids which stain

positively with Nile blue sulphate. Among these large-bodied cells are less obvious, elongated cells with oval, deeply staining nuclei. These cells appear to be endothelial in type and as noted above are occasionally seen to be intimately associated with the cells lining the capillaries. A few scattered, rounded cells, somewhat smaller than the vacuolated cells, are found to be multinucleated. Occasional small cysts filled with pink granular material are seen, as well as evidence of more generalized edema such as the separation of individual cells by similar material.

There is an abundant reticular network throughout the tumor outlining the capillaries, bridging between them, and running to the collagenous walls of some of the larger channels (Fig. 9). The latter contain no elastic tissue or any smooth muscle cells. No nervous or glial elements are found in the growth.

The tumor is apparently attached to, and growing into, the pia externally (Fig. 1). Internally, although it has a definite margin, it has no capsule and numerous capillaries of the neoplasm extend beyond its general border into the surrounding nervous tissue. Directly about the tumor the parenchyma is quite edematous and markedly degenerated and here there is considerable proliferation of microglia with the formation of compound granule cells. Beyond this zone of degeneration is an area in which there is hypertrophy and proliferation of astrocytes with multiplication of glia fibers. This zone is predominantly in the posterior columns and horns. The white matter of the lateral and anterior columns, especially the former, shows a considerable diffuse loss of myelin sheaths and axones with the presence of scattered compound granule cells. On the left side the anterior horn cells have almost all disappeared while on the right a good number are preserved.

Mural Nodule of Cerebellar Cyst: This growth also is quite vascular. Its vessels in general appear more regular and many are considerably more dilated, although all appear to be capillary in type. In some zones these vessels lie closely approximated and are packed with erythrocytes. In the more cellular areas the intervascular elements are predominantly polygonal, large-bodied or elongated narrow cells with concentrated oval nuclei. None of the lipoid-containing cells are seen here. There is considerable interstitial edema, as evidenced by the separation of the cells. The neoplasm, although fairly well circumscribed like the first lesion, shows the same minor

surface irregularity. The surrounding cerebellar tissue shows a moderate gliosis and some edema.

The wall of the cyst is lined by a narrow band of glia fibers. The cerebellar parenchyma external to it shows some signs of compression.

Tumor Attached to Cauda Equina: This is similar in all respects to the neoplasm in the cervical cord. It is surrounded by a narrow, collagenous connective tissue capsule.

Tumor in Thoracic Cord: This growth is somewhat more cellular than that in the cervical cord and correspondingly less vascular. Its vessels are all capillaries. The interstitial cells are only occasionally foamy. The majority are elongated or fusiform and have oval, deeply staining nuclei. The tumor is fairly small, well circumscribed and lies in the right posterior horn. Its margins are similar to those of the cervical lesion. About it there is a fairly wide zone of edema, mild degeneration and gliosis which includes most of the gray matter and the adjacent areas in the white columns.

Syringobulbia: Lower Medulla Near Junction with Cord: The pia is somewhat thickened and contains occasional lymphocytes. The stem is much increased in size and its architecture markedly disturbed. A large, roughly oval cavity with a number of narrow outpocketings is found occupying the central portion of the dorsal half of the stem. It lies just ventral to the obliterated central canal which is represented by a double row of polygonal and irregularly cuboidal cells. Its wall is a dense mass of glia fibers, heavier internally and less concentrated externally. Only occasional glia nuclei can be found in the central layer, whereas externally a fair number of fibrous astrocytes are present. The glia fibers, for the most part, run parallel with the margin of the cavity. The external layer contains a moderate number of hyperemic capillaries and one arteriole shows a perivascular infiltration of lymphocytes. There is considerable edema of the surrounding parenchyma with degeneration of ganglion cells, myelin sheaths and axones and scattered compound granule cells are present. A diffuse gliosis is observed in this zone. The external glial membrane is moderately thickened.

Microscopically this syrinx is found to reach down to a point on a level with the beginning of the tumor of the cervical cord.

Syringomyelia: The cavities found beginning just below the intramedullary cervical growth are microscopically similar in most re-

spects to those in the medulla. Their walls show a similar conformation and the parenchyma about them shows varying degrees of the same edema, degeneration and gliosis. This is true also of the extension of these cavities into the upper thoracic cord. In each case they do not seem to involve the central canal which is everywhere obliterated and represented only by irregular masses of ependymal cells, as in the lower medulla.

The syringomyelic cavities appearing just below the thoracic tumor vary somewhat from the above. Their walls are considerably thicker. The inner layer is composed of a much looser, edematous mass of glia fibers in which no cells or even nuclei can be discerned. External to this is a wide band of densely woven glia fibers containing scattered glia nuclei (Fig. 3). Outside this layer is an irregular zone of gliosis in which a fair number of fibrous astrocytes can be discerned. The parenchyma about these cavities shows more gliosis and less edema than is seen about the cervical and upper thoracic cavities.

Tumors in Left Adrenal: The three neoplastic masses are identical in appearance. They are composed of large, irregularly polygonal cells with indistinct cell outlines and large, round or oval, pale staining vesicular nuclei. These nuclei are rather uniform in appearance and have several poorly defined nucleoli. No mitotic figures are seen. The cells are arranged in small cords and nests which sometimes simulate alveoli. They are embedded in a rich vascular plexus, many small, freely anastomosing capillaries coursing about small groups of cells. In Zenker-fixed material the cytoplasm of the tumor cells is made up of finely granular, brown-staining matter, strongly resembling chromaffin. In formalin-fixed material this brown pigmentation is not seen. There are no areas of degeneration or necrosis in the tumor tissue although a few small hemorrhages and foci of small round cells are present. The tumor nodules are not encapsulated but are sharply limited from the surrounding adrenal cortex. No fat is demonstrated by sudan III stains. The Foot-Bielschowsky staining method reveals the presence of many fine reticulin fibers about the nests of cells.

Kidneys: The large white mass in the *right kidney* is composed of dense, avascular, pink-staining scar tissue containing a few scattered connective tissue nuclei, some large solid masses of calcium and several central cystic areas. The latter are not lined by epithelium,

but their walls are irregular and fibrous. They contain only a few extravasated erythrocytes.

One of the small masses in the *left kidney* resembles the large mass in the right, being composed of dense fibrous tissue. It contains several small cysts lined by flattened epithelium.

The second nodule in the left kidney is entirely different from the preceding two lesions. It is vascular and is composed of irregular cords of polygonal cells and tubular structures, many of which are filled with red blood cells (Fig. 10). A good number of the tubular structures are greatly distended and cystic. They are lined by a single layer of uniform cuboidal cells. A thin fibrous capsule surrounds most of the mass but in one area it is directly continuous with the adjacent renal cortex. In one part of the nodule many elongated, cylindrical cells with vacuolated cytoplasm are present.

Paraortic Lymph Node: In this lymph node, taken from the region of the left adrenal, are found two small masses of polygonal cells arranged in irregular cords (Fig. 11). These have foamy, lipoid-containing cytoplasm and round or oval, deeply staining nuclei. The cells strongly resemble normal adrenal cortical cells. No pigment is present in the cytoplasm of these cells.

Pancreas: The cysts in the pancreas are lined by flattened epithelium and encircled by a narrow band of fibrous tissue (Fig. 12). They contain small amounts of pink-staining granular débris. The acini immediately adjacent to the cysts are compressed and atrophic.

Summary of Autopsy Findings: Autopsy revealed a small cystic hemangioblastoma situated in the posterior portion of the central white matter of the right cerebellar lobe; a mild internal hydrocephalus; three hemangioblastomas of the spinal cord; syringobulbia and syringomyelia; congenital cysts of the pancreas and kidneys; a benign hypernephroma of the left kidney; an adrenal rest in a retroperitoneal lymph node; three paragangliomas of the left adrenal and a patent foramen ovale.

There was a terminal lobular pneumonia with acute fibrinous pleurisy and an acute splenic tumor.

Comment: Unfortunately we were unable to obtain any detailed clinical facts, pathological reports or specimens concerning the enucleated eyes beyond the information that they had been enucleated for detached retinae with terminal glaucoma. Almost all cases of angiomatosis of the retina end in retinal detachment which finally

necessitates enucleation of the eye. A majority of the cases of angiomatosis of the central nervous system, in the sense of Lindau's disease, are accompanied by angiomatosis of the retinae and it is extremely likely that the latter condition was present in our patient.

Discussion

Hemangioblastomas of the central nervous system are uncommon. They are most apt to occur in the third and fourth decades of life. The cerebellar hemangioblastomas comprise somewhat less than 1 per cent of intracranial tumors. Similar lesions of the spinal cord, stem and cerebrum are quite rare. Only 11 authentic cases of such tumors of the spinal cord are recorded in the literature. Lindau could find only 4 reports of comparable neoplasms in the stem, while Cushing and Bailey listed 4 published cases, which they felt fairly confident were instances of cerebral hemangioblastomas. Lindau claimed that they did not occur in the cerebrum. Recently, Rochat and Keller each described a case of a cerebral hemangioblastoma.

Roman's publication (1913) was the first reliable report of a spinal cord case. A single lesion was found in the thoracic cord. This was similar in most respects to the growths described in our case. Koch (1913) recorded during the same year multiple angiomatous tumors of the thoracic cord. Pinner (1914) shortly thereafter described a capillary hemangioblastoma which ran the entire length of the cervical cord. Tannenberg (1924), a decade later, recorded 2 cases. In 1 of these a vascular tumor was present in the upper lumbar cord and similar lesions in two nearby spinal ganglia, while the 2nd case showed a single specimen of the same type of growth in the lower portion of the lumbar cord. Schuback (1927) described a large capillary hemangioma of the thoracic cord. Kernohan, Woltman and Adson (1931) in a report of 51 cases of intramedullary tumors of the spinal cord mentioned four hemangioblastomas, two being present in a single case. No details as to location within the cord were given. The histological description was quite characteristic. The high percentage of angiomatous tumors in this series is unusual and does not correspond to the small percentage of such verified tumors in the literature. It may be purely coincidental that the hemangioblastomas bulk so large in the report of Kernohan *et al.* Russell (1932) described a capillary hemangioma of the cervical

cord. In the same year Guillain, Bertrand and Lereboullet recorded a case of multiple hemangioblastomas of the central nervous system.

The accompanying table gives some of the relevant data in these cases. Seven had single cord lesions and 5 multiple. The tumors occurred in all portions of the cord but showed some predilection for the cervical and lumbar enlargements. They occurred in the nerve roots and cauda equina as well. In all cases the tumors lay in the dorsal half of the cord, usually in the posterior columns, and showed a relation to the posterior septum. The neoplasm in the cervical portion in the case recorded here illustrates this point well. The growth in the posterior horn in the lower thoracic cord did not appear to have any relation to either the posterior septum or the pia. Four of the 12 cases showed an association of the cord lesions with cerebellar hemangioblastomas. The cerebellum is the favorite site for these neoplasms. It is interesting to note that 5 of these cases showed the associated lesions of Lindau's syndrome. Three of the cases revealed angiomatous growths in the stem. Each had a tumor in the medulla and 1 a tumor in the midbrain as well. There was a single record of concomitant involvement of the cerebrum.

Cushing and Bailey clearly differentiated between the angiomas and hemangioblastomas of the central nervous system in their monograph on blood vessel tumors of the brain. The angiomas they classified as malformations composed of arteries and veins, stressing the point that nervous tissue in various states of preservation was always found between the vessels of these lesions. The hemangioblastomas they considered to be true vascular neoplasms. In addition, a mass of dilated capillaries with nervous parenchyma between the vessels or single dilated tortuous arteries or veins were separately grouped as telangiectases.

The hemangioblastomas of the central nervous system appear to be true neoplasms, capable of growth which is sometimes fairly rapid. The analogous tumors of the retina can be directly observed in their growth. They do not metastasize nor are they apparently apt to spread along the ventricular system or subarachnoid space. A number of things point to a congenital factor in the development of these neoplasms. As Sabin has shown, the vascular network is laid down by mesodermal elements *in situ*, and it seems not unlikely that some maladjustment in this genesis may leave a nucleus for such a tumor. As Lindau has pointed out, the most common location

for the hemangioblastomas is in the rhombencephalon. The work of Karlefors has shown that in the third fetal month a vascular mesenchyme is found lying upon the posterior medullary velum. This is the anlage for the local meninges, the vascular plexus of the choroid of the fourth ventricle and of the vascular network in the areae postremae of the medulla. It is only toward the end of the third fetal month that the cerebellar hemispheres begin to develop. Lindau suggests that a portion of this original vascular plate lying in the midline might be pinched off and carried laterally into the developing hemispheres. This would account for the frequent location of the hemangioblastomas in the superficial and posterolateral portions of the cerebellum. The midline lesions and those in the medulla, which are always in its caudal portion, would be explained by the original position of the vascular plate.

As noted above, the hemangioblastomas of the spinal cord always occur in its dorsal half, very often in relation to the posterior septum. Bielschowsky, in discussing a teratoma of the cord, pointed out the possibility that portions of the surface membrane might be drawn down into the nervous parenchyma during closure of the medullary groove. This might later give rise to mesodermal growths. Tannenberg expressed a similar opinion in relation to a case of angioma of the cord.

The fact that the hemangioblastomas are often multiple and occasionally linked in Lindau's syndrome lends further support to the impression that there is a congenital factor involved in their origin.

The cerebellar hemangioblastomas may be cystic, solid, or partially cystic. The 11 cases reported by Cushing and Bailey were about evenly divided between the three types. Lindau gathered the reports of 24 cystic hemangioblastomas from the literature and added 16 of his own. The fact that he was specifically studying cerebellar cysts, however, resulted in a narrowing of the field, which led to the impression that cerebellar hemangioblastomas were almost exclusively cystic. Although predominantly so, they are not wholly of this nature. The spinal cord hemangioblastomas are all solid, although some are associated with syringomyelia, as seen in the table. We will revert to this point later in discussing the syringomyelia in our case. Lindau expressed the opinion that the cysts, both within the tumor and about it, were occasioned by circulatory disturbances in the growth giving rise to a plasmatic transudate. He

felt that the paucity of lymph channels in the nervous parenchyma did not permit ready resorption of this fluid and so cysts were formed. He ventured that the same was true of his series of cystic vascular gliomas. Cushing and Bailey, however, pointed out that extensive cystic formation was equally characteristic of the relatively non-vascular gliomas, particularly the fibrillary astrocytomas, so that the transudate cannot be attributed merely to the vascularity of the lesion. That the cyst fluid is a transudate and not simply due to degeneration of the tumor proper is evidenced by the rapidity with which such cysts refill after tapping, and the chemical resemblance of the fluid to plasma. Cushing and Bailey call attention to the fact that both angiomatous and gliomatous cysts usually have a small mural nodule of tumor such as was present in the cerebellar lesion of the case reported here. That the cystic fluid probably originates in these nodules is evidenced by the failure of such cysts to refill when the mural nodule has been removed. The causes of this cyst formation are, however, not clearly established. Of two similar hemangioblastomas of the cerebellum in Koch's case one was cystic and the other not.

Histologically the cervical hemangioblastoma in the case described here is quite characteristic of such tumors. It is predominantly capillary, although there are a considerable number of intervascular cells. Some of the reported hemangioblastomas present purely capillary zones in which no such intervening cells are present. Others are quite cellular. There appears to be an intimate relation between these interstitial cells and the lining of the capillaries, and Cushing and Bailey suggest that they arise by endothelial hyperplasia. The lipoid content of many of the intervascular elements, which was so striking in the cervical and cauda equina tumors in our case, has been variously explained. Tannenberg was of the opinion that circulatory disturbances reduced the nutrition of the tumor cells so that they underwent a degenerative, fatty metamorphosis. Lindau, however, pointed out that the tumor cells stained well and did not appear degenerated. He suggested that in the formation of a cyst in the neighborhood of a hemangioblastoma there must be a slow destruction of nervous tissue. The lipoids thus liberated are taken up by the endothelial elements in the tumor. The myelomalacic area about the cervical cord tumor in the case described here might be the source of the lipoid material in the solid tumors. To

TABLE I

Hemangioblastomas of Spinal Cord

Cases listed by authors	Single or multiple in cord	Location in cord	Coincident hemangioblastomas of			Accompanied by syringomyelia	Associated with Lindau's syndrome
			cerebellum	stem	cerebrum		
Roman	Single	Thoracic cord	....	....	....	....	....
Koch	Multiple(2)	Cervical and thoracic cord	+ (2) One in each hemisphere	....	....	....	+
Pinner	Single	Cervical cord	....	....	....	+ Cervical to upper lumbar	....
Tannenberg I	Multiple(3)	Lumbar cord (1) Adjacent spinal ganglia (2)	+ (2)	+ (1) Medulla	....	+ Upper cervical	+
Tannerberg II	Single	Lumbar cord	....	....	....	+ From cervical through lumbar	....
Schuback	Single	Thoracic cord	....	+ (1) Fourth ventricle through medulla to C–2	....	+ Almost entire cord	+
Kernohan *et al.* I	Single	Not given	....	....	....	....	....
Kernohan *et al.* II	Single	Not given	....	....	....	....	....
Kernohan *et al.* III	Multiple(2)	Not given	....	....	....	+	+
Russell	Single	Cervical cord	....	....	....	+ Cervical through thoracic	....
Guillain *et al.*	Multiple	Cauda equina and about lumbosacral cord	+ Multiple	+ Multiple	+ Right ventricle	....	....
Wolf and Wilens	Multiple	Cervical and lumbar cord and cauda equina	+	....	....	+ Cervical through lumbar	+

support his opinion Lindau pointed to the phagocytosing power of cells of endothelial origin. Similar tumors elsewhere in the body where lipoids are not so abundantly liberated in degenerative processes, as in the nervous system, do not show these large lipoid-containing cells. The occasional mitoses and small multinucleated giant cells encountered in the hemangioblastomas give evidence of their active growth. The reticulin network outlining the capillaries and forming intercapillary bridges is quite characteristic. Occasionally the intervascular cells become so prominent in a hemangioblastoma that they dominate the picture, although transitions can be found to capillary areas. Again the capillaries may become dilated so that they form large irregular sinuses. The latter condition was present to some degree in our cerebellar tumor. On the basis of these variations Cushing and Bailey classified the hemangioblastomas as predominantly capillary, cellular or cavernous. They described two cellular hemangioblastomas of the cerebellum and referred to another of the retina reported by Brandt. These tumors have many areas in which big epithelioid, polygonal, cuboidal and columnar cells are gathered in large clusters and columns. These cells have no processes or fibrils. Many contain considerable amounts of lipoid. This type of hemangioblastoma, however, is evidently quite rare. The capillary type with varying numbers of intervascular cells is the common variety.

From the table it may be seen that 5 of the 12 cases of spinal cord hemangioblastomas were associated with Lindau's syndrome. Beside the angiomatosis of the central nervous system in our case there were, as noted above, congenital cysts of the pancreas and kidneys, a benign hypernephroma of the left kidney, an adrenal rest in a retroperitoneal lymph node, and a paraganglioma of the left adrenal. As has been stated, it is extremely likely that retinal angiomas were present in this case, although we lack anatomical confirmation of this point.

Brandt, in his study of angiomatosis of the retinae, or von Hippel's disease, gives the average age of onset of symptoms as 25 years, with some cases beginning in childhood but none apparently after 45. The average age of onset of symptoms in angiomatosis of the cerebellum, as given by Lindau, is 32 years. When both are present in Lindau's syndrome the angiomatosis of the retinae is the first to give symptoms, while the central nervous system lesions are not in evi-

dence until a good deal later. In the case recorded here the eye disturbances began at the age of 21, while the cerebellar and cord symptoms did not appear until the patient was 32.

Lindau points out a familial disposition to angiomatosis of the retinae and similarly of Lindau's syndrome. Kufs has gathered data on this point and calls attention to the fact that unaffected members of the affected family may transmit the disease.

In the case described here the father had died of brain tumor at the age of 36 and the mother of "spinal meningitis" at 28 years of age. A twin brother and sister had died at birth. Although no details are known as to the type of tumor which the father had, it is possible that it was an hemangioblastoma. It is uncertain whether the conditions in the other three were related.

Angiomatosis of the retinae has been described twice as frequently in men as in women, while angiomatosis of the central nervous system occurs with about equal frequency in the two sexes.

Lindau considers a cystic pancreas one of the most constant features of his syndrome. Very often the cysts may permeate the entire pancreas and in 2 of the recorded cases a glycosuria was present. These pancreatic cysts are lined by a single layer of cuboidal cells which may become flattened and endothelial-like, as was true in our case. Some cysts are lined by columnar epithelium and others show papillary proliferation. Both Berblinger and Lindau consider them to be dysontogenetic in origin. According to Lindau the work of Siwe shows that in the second and third fetal months the branching anlage of the pancreas and a vascular mesenchyme from the dorsal mesentery intertwine in growth. A disturbance in the equilibrium between the mesodermal and epithelial tissues might lead to the snaring-off of clusters of epithelial cells from which the cysts could later develop.

Next in frequency, as concomitant lesions in his syndrome, Lindau places the malformations and tumors of the kidneys and adrenals. The cystic lesions of the kidneys in our case are undoubtedly congenital in origin and similar cysts were described in many other cases of this disease, 10 of the original 15 gathered by Lindau having them. Hypernephromas were present in 6 of these 15 cases and such a tumor was present in the left kidney of our case. The adrenal rest in the lymph node is quite unusual. The benign appearance of these nodules made it certain that they were not metastases from the

kidney and were additional congenital lesions. The paragangliomas of the adrenal in our case are the first that have been encountered in a case of Lindau's disease. They are typical examples of this uncommon type of tumor.

The familial occurrence and the presence of coincidental lesions in many organs prompted Lindau to consider the syndrome named for him as one in which there were many congenital rests and malformations referable to one of the embryonic layers. This he took to be the mesoderm and suggested that the developmental disturbance probably occurred during the third fetal month. At this time there occur vascularization of the retina, formation of the vascular mesodermal roof-plate of the fourth ventricle and ingrowth of mesodermal elements into the pancreas. Maldevelopment at this time may lead to the formation of renal cysts. He called attention to the similarity of the condition to neurofibromatosis and tuberosclerosis. In neurofibromatosis there are multiple tumors of the peripheral and sometimes central nervous system accompanied by skin pigmentation. In tuberosclerosis there are focal glioses of the brain, gliomas, rhabdomyoma of the heart, embryonal renal tumors and renal cysts. In both conditions there may be occasional retinal tumors.

As noted in the table of spinal hemangioblastomas, 7 of the 12 cases showed an associated syringomyelia. This is not an uncommon accompaniment of intramedullary cord tumor. Of the 51 intramedullary tumors of the cord reported by Kernohan *et al.*, 10 came to autopsy and 9 were true neoplasms, 1 being a tuberculoma. Five of these 9 cases were associated with syringomyelia. One was the hemangioblastoma included in our table, 2 were ependymomas, 1 was a medulloblastoma, and the last was an oligodendroglioma. In each of these cases the syringomyelia was described as quite characteristic. The cavities were extensive, surrounded by gliosis and not lined by ependyma.

This association of syringomyelia with spinal cord tumors has been explained in various ways. Lindau is of the opinion that these cavities in the cord are simply elongated cysts similar to the cysts so commonly encountered about cerebellar hemangioblastomas and due to transudation from the vessels of the tumor. He believes that they show only a superficial resemblance to true syringomyelia. The circulatory disturbances in vascular tumors cause edema which spreads

in the nervous parenchyma about the tumor. Edema of the intramedullary hemangioblastomas and of the surrounding parenchyma was quite definite in our case. The spread of the edema fluid occurs, as in hematomyelia, in narrow irregular columns up and down the cord, usually for long distances. Where the fluid collects cavities form, the nervous and glial tissues being compressed. The pressure of the fluid causes a reactive gliosis producing the wall of the syringomyelic cavity. It is true that the syringomyelic cavities in these cases associated with cord tumors usually course from the tumor, stretching away both above and below it. The syringomyelia of the cervical cord and the syringobulbia with which it is continuous appear to be definitely related to the hemangioblastoma in the upper cervical cord. The cavities in the lower thoracic region and lumbar cord seem equally related to the neoplasm of the lower thoracic cord. This is rather small and the cavities large. Many cystic cerebellar hemangioblastomas, however, have small mural nodules and quite a large cyst. Kirch also points out that solid gray glial columns, such as are considered to antedate the cavity in many true syringomyelias, can be found in relation to intramedullary cord tumors. This is true in Schuback's case in which such solid glial columns were found flanked by cavities. Kirch suggests that in these cases no collections of edema fluid have formed, a more diffuse infiltration of the tissue by the serous transudate having occurred. The occurrence of syringomyelia in relation to such tumors as the medulloblastoma and oligodendroglioma of the cord reported by Kernohan *et al.*, is difficult to explain on the basis of a circulatory disturbance in a vascular tumor with transudation. The same was true, as noted above, in attempting to explain the genesis of neoplastic cerebellar cysts on the same basis when one considers the cysts accompanying the relatively non-vascular fibrillary astrocytomas of the cerebellum. Kernohan *et al.*, however, in discussing the syringomyelia in their case of spinal cord hemangioblastoma were of the same opinion as Lindau and Kirch. Tannenberg also expressed the opinion that the syringomyelia in these cases is comparable to the cysts which form in relation to tumors of the central nervous system. He believes them to be due to softenings in the region of such neoplasms with resultant cavity formation and gliosis, rather than a mere transudation, fluid collection and tissue compression. He considers the necroses to be due both to circulatory disturbances locally and to

toxins elaborated by the tumor. That considerable destruction can occur about spinal cord hemangioblastomas was evidenced in the degeneration about the intramedullary tumors in our case and these degenerated zones bridge from tumor to syringomyelia.

Russell likewise believes that anemic or hemorrhagic softenings due to the presence of a tumor in the cord may give rise to the syringomyelia. She quotes Cornil and Ranvier for evidence that softening following trauma follows the same distribution as hemorrhage in the cord. A column of softened tissue in the posterior columns and horns, parallel with the long axis of the cord, may extend for long distances. Finally a cavity with a glial wall is formed. To prove that such softenings occur secondary to cord tumors she gives the details of an autopsy from her own laboratory. It was a case of cord metastasis in the first and second lumbar segments from a carcinoma of the lung. There was hemorrhagic softening of the cord to the tenth, and anemic softening to the sixth thoracic segment. Below the tumor the rest of the lumbosacral cord was involved in hemorrhagic softening.

Another explanation of the association of angiomatous neoplasms with syringomyelia is that they are coincident, multiple, congenital anomalies. Bielschowsky expressed this opinion and Jonesco-Sisesti more recently was strongly in its favor. Both adduce the evidence of the conjunction of teratomas and teratoid tumors of the cord with syringomyelia. Furthermore, the occurrence of the syringomyelia with multiple congenital malformations, such as occur in Lindau's disease and in neurofibromatosis, would be in favor of this theory. Our own case and 4 others listed in the table showed this association. A number of the reported cases and 2 of those listed in the table, however, do not show such congenital abnormalities.

A final possibility is that hemorrhages from intramedullary tumors, in particular hemangioblastomas, may produce hematomyelia which results in a syringomyelia. Russell discusses this theory and points out that Ohlmacher's case of a cavernous angioma of the cervical cord was accompanied by a hematomyelia which extended for some distance above and below the tumor. She quotes a case of her own, an ependymal glioma of the lumbar cord associated with syringomyelia. There was evidence of an old hemorrhage in the borders of the syringomyelic cavity and in the walls of a cyst within the tumor. Russell believes that this may be the cause of the associ-

ation in some cases, but most often when there is hemorrhage it is secondary to the circulatory disturbance with necrosis.

In our case the syringomyelia is anatomically quite typical and in no wise distinguishable from similar lesions of this nature. Its wall resembles that of the cerebellar cyst and in a sense the syringomyelic cavities can be considered "cysts" related to the spinal cord tumors. They are intimately associated with the neoplasms, being ranged about them. The markedly edematous areas with the often intense accompanying degeneration are directly continuous with the syringomyelia, or contiguous to the tumors. They point to a local vascular disturbance with transudation.

From the evidence of our own material, therefore, we believe these cavities in the cord to be true syringomyelia and yet comparable to the similar cerebellar cysts and similar cysts elsewhere associated with tumor. The most plausible explanation of their formation is that a columnar edema and necrosis occurs secondary to circulatory disturbances produced by the tumor, with subsequent cavity formation and mural gliosis.

Summary

A case of multiple hemangioblastomas of the spinal cord forming part of Lindau's syndrome is presented. These intramedullary tumors are associated with a syringomyelia and syringobulbia. The other lesions are a cystic cerebellar hemangioblastoma, congenital cysts of the pancreas and kidneys, a benign hypernephroma of the left kidney, an adrenal rest in a retroperitoneal lymph node and three paragangliomas of the left adrenal.

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DESCRIPTION OF PLATES

PLATE 132

FIG. 1. Hemangioblastoma of cervical cord. Hematoxylin-eosin stain.

FIG. 2. Hemangioblastoma of lower thoracic cord. Hematoxylin-eosin stain.

FIG. 3. Syringomyelia. Lumbar cord. Phosphotungstic acid hematoxylin stain.

FIG. 4. Syringobulbia. Lower medulla. Phosphotungstic acid hematoxylin stain.

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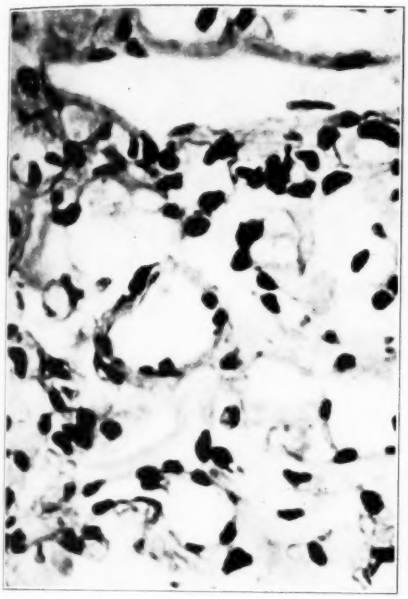
PLATE 133

FIG. 5. Capillary zone in cervical cord hemangioblastoma. Hematoxylin-eosin stain. × 720.

FIG. 6. Capillary zone in thoracic cord hemangioblastoma. Hematoxylin-eosin and Laidlaw stains combined. × 450.

FIG. 7. Pseudoxanthomatous cells between the capillaries in a cellular area of the cervical cord hemangioblastoma. Hematoxylin-eosin stain. × 720.

FIG. 8. Pseudoxanthomatous cells in thoracic cord hemangioblastoma. Phosphotungstic acid hematoxylin stain. × 720.



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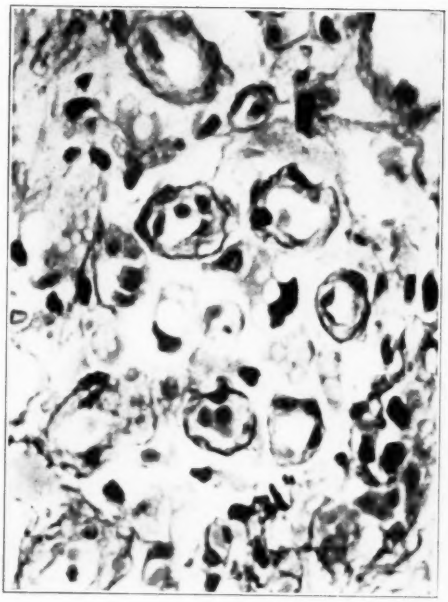

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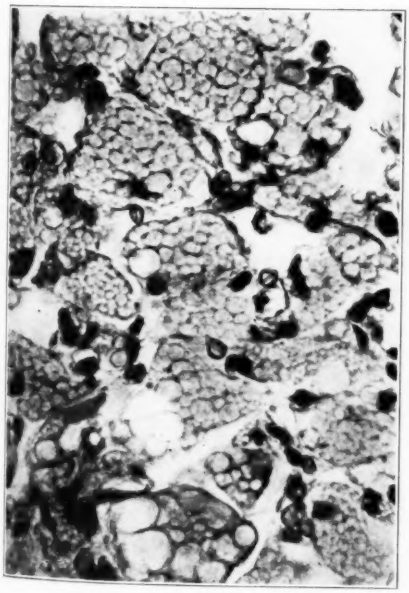

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PLATE 134

FIG. 9. Capillaries in cervical cord hemangioblastoma. Note tendency to radiate from the large, thick-walled channels. Laidlaw stain. × 80.

FIG. 10. Benign hypernephroma of the left kidney. Hematoxylin-eosin stain. × 100.

FIG. 11. Adrenal rest in retroperitoneal lymph node. Hematoxylin-eosin stain. × 100.

FIG. 12. Cysts in pancreas. Hematoxylin-eosin stain. × 80.

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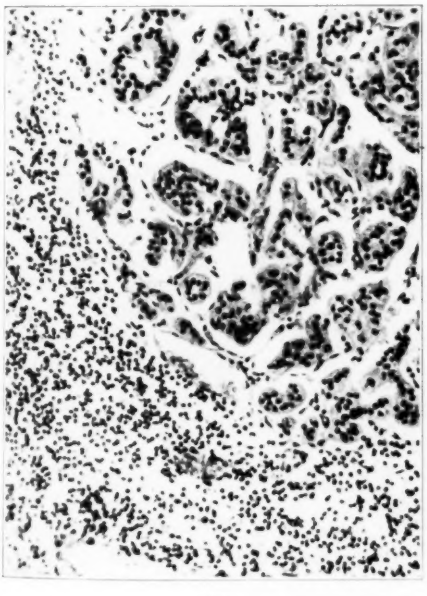

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XI